REMARKS

Claims 1, 3, 4, 6-10, 22-28 and new claim 29, appear in the application for the Examiner's reconsideration. Claim 28 has been amended to correct certain minor informalities as suggested by the Examiner. New claim 29 is the independent form of original claim 5, which is now cancelled. Claim 2 has also been cancelled and its features incorporated into claim 1. As no new matter has been introduced, the entry of the claim amendments and new claim at this time is warranted.

The Examiner noted that a certified copy of the original foreign application must be filed with the U.S. Patent and Trademark Office in order to perfect the priority claim. In response, applicants note that a certified copy of that priority document was submitted on February 28, 2003. Acknowledgement of receipt of that copy would be appreciated.

The abstract was objected to for not completely describing the disclosed subject matter. Specifically, the Examiner requests that complete sentences be furnished and that the full names of the particular species used be included. In response, Applicants have amended the abstract to correct those minor informalities. Thus, the submission of the substitute abstract overcomes this objection.

The specification was objected to for having improper margins. In response, Applicants are submitting herewith a substitute specification which has been reprinted with proper margins. Thus, this objection has also been overcome.

The specification was further objected to for the inclusion of the plural terms "Streptococci, Lactobacilli, and Actynomyces." In response, Applicants have replaced those terms with the proper singular ones "Streptococcus, Lactobacillus, and Actinomyces."

The Examiner further objects to the references "X17390," "X14490," and "X53657" as being unclear. The Examiner inquires whether these are GenBank accession numbers. Applicants respectfully note that the specification indeed identifies these as GenBank accession numbers in the last paragraph on page 8. The Examiner states that if they are GenBank numbers, then an internet address is required. Applicants respectfully point out that these are not documents retrieved from the internet. Thus, a requirement of an internet address is improper here.

The Examiner still objects to the terms "quark," "coffee cream" and "rennetted milk" as lacking clear definitions. Applicants respectfully traverse. Applicants submit herewith U.S. Patent No. 6,365,205, which includes the term "quark" (col. 1, line 8); U.S. Patent No.

6,383,550, which includes the phrase "coffee cream" (col. 8, line 5); and U.S. Patent No. 3,991,667, which includes the phrase "rennetted milk" (col.1, line 44). None of these patents provides a definition of the terms which were objected to by the Examiner as being unclear. This indicates that one skilled in the art is well acquainted with the meanings of these terms, and the definitions of the same are unnecessary. Thus, the Examiner's objections have been overcome.

The term "FUM medium" was objected to in the office action. As this term is dully understood to skilled artisans as referring to a Fluid Universal Medium, the objection should be withdrawn.

The office action also objects to the term "Belliker". In response applicants note that this term refers to the product that is defined in example 1: it is prepared by dissolution in 1 l water of 20 g tryptone, 5 g yeast extract, 2.5 g gelatine 5 g dextrose, 5 g sucrose, 5 g lactose, 4 g NaCl, 0.5 g Ascorbic acid, and 10 g beef extract. As this is clear from the example, the objection should be withdrawn.

Claim 2 was objected to for some minor informalities. Specifically, the Examiner states that the range 5.5 to 5.7 in claim 2 seemed incorrect. Although claim 2 has been cancelled, applicants have amended claim 1 to recite that the pH range is 5.5 to 7, as suggested by the Examiner and supported by the specification. Thus, the Examiner's objection has been overcome and should be withdrawn.

Claim 5 was objected to for depending from a rejected claim. In response, Applicants have rewritten claim 5 in independent form. Thus, the Examiner's objection has been overcome. Since claim 5 was not otherwise objected to by the Examiner, it is now believed to be in condition for allowance.

Claims 1-3, 6-10 and 23-28 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Specifically, the Examiner states that the phrase "lactic bacteria that are not part of the resident microflora of the mouth" is unclear as to its exact metes and bounds. Applicants traverse, since it is well known as to which bacteria are and are not resident in the mouth. Also, several genera are mentioned in the background section, while only specific Streptococcus species are listed. Although particular species of other lactic bacteria that are not part of the resident microflora or the mouth, e.g., Lactobacilli, Veillonella, etc., are not listed, they are well-known in the art and require no specific mention or exemplification.

Claims 1-4, 6-10 and 23-28 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Specifically, the Examiner states that the term "low acidifying" is a relative term and that it renders the claim indefinite. Applicants respectfully traverse. The specification of the present invention clearly defines "low acidifying" as meaning the lactic bacterial according to the present invention "are less acidifying than pathogenic strains" and "contribute to the a pH in the oral cavity of about 5.5 to 7 "(p. 8, first full paragraph). In addition, claim 1 has been amended to specifically recite this preferred pH range. Thus, the Examiner's rejection has been overcome and should be withdrawn.

Claims 2 and 6 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Specifically, the Examiner objects to the term "about." Applicants respectfully traverse. The use of the term "about" is explicitly endorsed by the MPEP. Section 2173.05(b) cites *Ex parte Eastwood*, 163 USPQ 316 (Bd. App. 1968), as holding that the term "about" used to define the area of the lower end of a mold as between 25 to about 45% of the mold entrance was clear, but flexible. Thus, the use of the term "about" in the present invention is entirely proper and the Examiner's objection has been overcome and should be withdrawn.

Claim 3 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the inclusion of the term "of diary [Applicants believe the Examiner meant "dairy"] origin." Applicants respectfully traverse. The term "of dairy origin" clearly means that the lactic bacteria are derived a dairy product, which in turn requires no definition as a common word in everyday parlance. This term is commonly known and used in the art so that there is no confusion over its meaning. Thus, the Examiner's rejection has been overcome and should be withdrawn.

Claim 8 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the references to gene numbers. As explained above, the reference to gene numbers are GenBank accession numbers and they are definite in their meanings. Thus, the Examiner's rejection has been overcome and should be withdrawn.

Claims 9 and 24 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Examiner states that is unclear what the scope of "milk derivative" is. Applicants respectfully traverse. The phrase "milk derivative" is well defined in the art and does not require any definition. It has already been included in other patent documents, such in claim 5 of U.S. Patent No. 4,339,464, a copy of which is enclosed herewith, without a

specific definition in the specification. This is because the term is known and used conventionally without controversy over its meaning. Thus, the Examiner's rejection has been overcome and should be withdrawn.

Claims 10 and 26 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the inclusion of the phrase "renneted milk." As explained above, renneted milk is another term that is well-known in the art and requires no further definition. Thus, the Examiner's objection has been overcome and should be withdrawn.

Claims 23-26 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Examiner states that the phrase "to provide a pH of at least 5.5" is unclear because it is not clear whether the pH 5.5 is a higher limit or a lower limit. Applicants respectfully traverse. Although Applicants are aware of the potential confusion due to the fact that a higher acidity entails a lower pH value, the phrase "a pH of at least 5.5" clearly refers to a pH value, not acidity or basicity, which equals or exceeds 5.5. This is also supported by the recitation of the pH values between 5.5 and 7 in claim 1 as well as in numerous places in the specification. Thus, there is no ambiguity: the numerical value of 5.5 is the minimum and higher or greater numerical values are contemplated by the claim, up to the maximum pH value of 7 that is recited in claim 1. The Examiner's objection has been overcome and should be withdrawn.

Claims 27-28 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Examiner objected the terms "oil soluble antioxidant," "abrasive," "quark," and "coffee cream." Applicants respectfully traverse. As explained above, the terms "quark" and "coffee cream" are well known in the art and require no definition. The other two terms "oil soluble antioxidant" and "abrasive" are also well known, as demonstrated by their use in the claims of other patent documents such as U.S. Patent No. 5,646,186, and No. 6,261,540, respectively. The latter patent specifically mentions "an orally acceptable dental abrasive," and is a closely related field to the present invention. Neither patent contains any definition of those terms in either the specification or the claims due to the well known nature of those terms. As both terms are well known in the art, no such definition is required. Thus, the Examiner's rejection has been overcome and should be withdrawn.

Claim 28 was rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to the skilled artisan that Applicants had possession of the invention when the application was filed. Specifically, the Examiner objects to the term "salad dressing" on the ground that only

"sweet salad dressing" was included in the original claims. In response, Applicants have amended claim 28 to recite "sweet salad dressing." Thus, the Examiner's objection has been overcome and should be withdrawn.

Claims 1-4, 6-10 and 23-28 was rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to the skilled artisan that Applicants had possession of the invention when the application was filed. The Examiner cites University of California v. Eli Lilly, 119 F.3d 1559 (Fed. Cir. 1997), as holding that a written description of invention involving chemical genus, like description of chemical species, requires precise definition, such as by structure, formula, or chemical name, of claimed subject matter sufficient to distinguish it from other materials.

Applicants respectfully traverse. First of all, the University of California v. Eli Lilly case relates to an entirely different subject matter than that of the present invention. That case relates to patents claiming DNA. As one skilled in the art would certainly appreciate, the exact three dimensional structure of a DNA is not readily deductible even from the DNA sequence. Thus, the Federal Circuit understandably would imposing a higher standard in adequately describing the DNA. This is confirmed by the portion in the University of California v. Eli Lilly case quoted by the Examiner which clearly treats claims involving chemical materials and genetic materials entirely differently (see Office Action, pp.8-9). Since the present invention relates to chemical/biological materials, i.e., lactic bacteria, the requirements of written description for DNA which is genetic in nature is not applicable.

Even assuming arguendo that the requirement of University of California v. Eli Lilly were to apply, the description of the present invention would still be sufficient, contrary to what the Examiner asserts. As the Examiner quotes, "the written description of invention involving chemical genus, like description of chemical species, requires precise definition, such as by structure, formula, or chemical name, of claimed subject matter sufficient to distinguish it from other materials." The names of the lactic bacteria of the present invention are explicitly described in the specification and in claims 4-5. Even in the case wherein the subject matter that is DNA, University of California v. Eli Lilly states that "adequate written description of DNA that is subject of patent requires precise definition, such as by structure, formula, chemical name, or physical properties, not mere wish or plan for obtaining claimed chemical invention." Here, the property of the lactic bacteria, i.e., that they are low acidifying, was clearly taught, in addition to their names.

Moreover, applicants have not invented a bacteria or other complex organism, but instead have invented a composition of certain ingredients and its method of use. The skilled artisan has none of the problems noted in the previous decision, so that the rejection is simply not applicable to the present claims or specification. Thus, the description of the present invention is sufficient under the law and the Examiner's rejection should be withdrawn.

Claim 7 was rejected under 35 U.S.C. 112, first paragraph as lacking enablement. The Examiner states that the specification, while being enabling for methods of using lactic bacteria modified to contain one of the three genes in claim 8, does not reasonably provide enablement for methods using lactic bacteria modified in other ways to cause improved adhesion and/or to be less acidifying than the resident microflora. Applicants respectfully traverse.

First of all, the MPEP explicitly points out that the Examiner has the initial burden to establish a reasonably basis to question the enablement provided for the claimed invention. (MPEP, section 2164.04). Secondly, the factors to be considered when determining the satisfaction of the enablement requirement include, among other things, the state of the prior art; the amount of direction provided by the inventor; the existence of working examples. In the present invention, Applicants explicitly teach that the modification to the lactic bacteria can be achieved in many ways. The specification further teaches that the modification is preferably achieved according to the protocols described in Boumerdassi et al., Plattecuw et al., and Ito et al (p.9, first full paragraph). Furthermore, the specification provides specific examples of how the genetic modification of the lactic bacteria can be achieved, i.e., by insertion of the X17390, the X14490 or the X53657 gene, in order to improve adherence to the pellicle of the teeth or to be less acidifying than the resident microflora in the mouth (p.8, last paragraph). Since the specification provides both adequate guidance and specific examples of the modification, it is sufficiently enabling as to claim 7. Thus, the Examiner's rejection has been overcome and should be withdrawn.

Claims 1-4, 6, 9 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 92/14475 by Madinier (hereafter "Madinier"). Applicants respectfully traverse.

The present invention teaches a method of treating or preventing dental caries, dental plaque, and periodontal infection in a humans or animals comprising administering to the oral cavity of a human or animal one or more lactic bacteria that are not part of the resident microflora of the mouth, that are low acidifying, and that are capable of adhering directly to

the pellicle of the teeth to displace from the teeth or prevent attachment to the teeth of cariogenic strains of bacteria that are resident microflora of the mouth (see claim 1).

As explained in the specification of the present invention, lactic bacteria that are not part of the resident microflora of the mouth have never been shown to be capable of directly adhering to the pellicle of teeth. The lactic bacteria of the present invention, due to their ability to adhere directly to the pellicle of the teeth, could advantageously exert an inhibitory activity against the growth of the resident microflora (p.4, third full paragraph).

The lactic bacteria of the present invention is also low acidifying. This is advantageous because organic acids produced by oral bacteria during the fermentation process directly cause dental caries. These acids attack the hard tissue of teeth with the consequent release of ions such as calcium, phosphate, carbonate, magnesium, fluoride, and sodium (p.2, second full paragraph). By providing a pH in the oral cavity of about 5.5 to 7, the lactic bacteria of the present invention would provide a saliva that is saturated with calcium, so that calcium liberation from the tooth is prevented.

Madinier teaches prophylactic ferments for combating dental caries on account of their competitive ecological properties in relation to possible cariogenic strains and agro-food properties. The prophylactic ferments consist of different bacteria capable of entering into competition with other oral flora bacteria, such as avirulent strains of *Streptococcus, Latobacillus*, and *Stomatococcus*, or other avirulent bacterial or mutant species corresponding to the oral health (Madinier, Abstract). As the Examiner concedes, Madinier does not teach the pH characteristics of the lactic bacteria of the present invention that are recited in claim 1. Applicants respectfully point out that Madinier fails to teach lactic bacteria that are capable of adhering directly to the pellicle of the teeth. Since Madinier fails to teach at least two critical features of the present invention, it does not anticipate the latter. Thus, the Examiner's rejection should be withdrawn.

Claims 1-4, 6 and 28 were rejected under 35 U.S.C. 102(b) as being anticipated by Busscher et al. (hereafter Busscher). Applicants respectfully traverse.

Busscher sets out to determine whether biosurfactant release by *S. thermophilus* might constitute a mechanism by which the indwelling, silicone rubber voice prostheses can be prolonged. It teaches an adhering *S. thermophilus* B strain found in Turkish yogurt that interfere with yeast adhesion in the oropharynx by virtue of placing a biosurfactant that inhibits adhesion of this yeast that naturally colonizes voice prostheses. Busscher does not

teach lactic bacteria which are low acidifying and which are capable of adhering directly to the pellicle of the teeth.

In contrast, the present invention relates to a method of treating or preventing dental caries, dental plaque, and periodontal infection comprising administering to the oral cavity of a human or animal one or more lactic bacteria that are not part of the resident microflora of the mouth, that are low acidifying, i.e., having a pH of between 5.5 and 7. The lactic bacteria of the present invention are capable of adhering directly to the pellicle of the teeth to displace from the teeth or prevent attachment to the teeth of cariogenic strains of bacteria that are resident microflora of the mouth. Unlike Busscher, the present invention does not relate to inhibiting adhesion of a yeast that naturally colonizes voice prostheses.

Since Busscher relates to a different field than the present invention does, also it fails to teach critical features of the present invention, it does not anticipate the present invention. The Examiner's rejection has been overcome and should be withdrawn.

In view of the above, it is believed that the application is now in condition for allowance, early notification of such would be appreciated. Should the Examiner not agree, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the claims.

Respectfully submitted,

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INCORPORATION OF EXOGENOUS LACTIC BACTERIA INTO THE ORAL MICROFLORA

ABSTRACT

The present invention provides compositions for the prophylaxis or treatment of dental caries, dental plaque, and periodontal infection that include lactic bacteria that are not part of the resident microflora of the mouth, that are low acidifying, and that are capable of adhering directly to the pellicle of the teeth. Preferably, the lactic bacteria of the include one or more of *Streptococcus thermophilus, Lactococcus lactis subsp. lactis, or Lactococcus lactis subsp. lactis biovar diacetylactis.* The compositions are used in methods of treating or preventing dental caries, dental plaque, and periodontal infection.

INCORPORATION OF EXOGENOUS LACTIC BACTERIA INTO ORAL MICROFLORA

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of the U.S. national phase designation of PCT application no. PCT/EP99/05473, filed July 26, 1999, the entire contents of which are incorporated herein by reference thereto.

FIELD OF THE INVENTION

The present invention relates to the incorporation of exogenous lactic bacteria into the oral microflora for the prophylaxis or the treatment of dental caries, dental plaque, and periodontal infection.

BACKGROUND OF THE INVENTION

The mouth (oral cavity) contains resident and non-resident microflora. The resident microflora includes microorganisms that are able to establish a more or less permanent residence on the oral surfaces. These bacteria are mainly localized on the tongue, the buccal mucosa, and the teeth while the gingiva, lips, checks, palate, and floor of the mouth only support a very sparse microflora.

On the tongue and the buccal mucosa, the natural resident microflora includes microorganisms selected from Streptococcus, Veillonella, Bacteroides, and Haemophilus. On the teeth, Streptococci, Lactobacilli and Actynomyces predominate but a variety of Gram positive and negative cocci and rods can be also found.

For example, Frandsen et al. showed that S. *sanguis* predominates on the buccal mucosa but its primary habitat is the surface of teeth, that S. *gordonji* grows in the mature supragingival plaque, and that S. *oralis* and S. *mitis* grow in the initial dental plaque (Oral Microbiol. Immunol., 6, 129-133, 1991). Strains belonging to the mutans group are localized on teeth (S. *criscetus, S. downei,* S. *ferus,* S. *macacae,* S. *mutans, S. rattus, S. sobrinus).* Strains belonging to the *S. milleri* group predominate in dental abscesses (S. *anginosus, S. constellatus, S. intermedius)* (Bentley et al., Int. J. System. Bacter. 1991, 41, 487-494; Wood et al., The Genera of Lactic Acid Bacteria, Blackie Academic and Professional, Chapman & Hall, W. H. eds., 1995).

Many of these microorganisms are innocuous commensal microorganisms, but a lot of them have been recognized as being the etiologic agent responsible for several

diseases (Hill, M. J. and Marsh, P. D. eds. Human Microbial Ecology, 1990, CRC Press, Boca Raton Florida, USA)

Dental plaque is a film that forms on the surface of teeth consisting of bacterial cells in a matrix of extracellular polysaccharide and salivary products. Immediately after eruption, the teeth are covered with an amorphous layer of saliva, the acquired enamel pellicle (AEP), that is about 1.3 μm thick and cannot be removed by normal tooth brushing. The deposition of bacteria on teeth immediately follows the formation of the AEP and plaque becomes evident in 8-12 hours as a multi-layered structure. The first layer consists of bacteria (earliest colonizers) that attach to teeth, mainly via specific adhesion-receptor recognition, and forms a substratum for the second colonizers that adhere one to the other by analogous specific binding or by simple juxtaposition. Plaque cohesion is essentially guaranteed by three mechanisms: the presence of a salivary pellicle on the outer bacteria layer, the specific co-aggregation among the different bacterial species, and the glucans synthesized by the bacteria that remain entrapped in the plaque matrix (Skopek et al., Oral Microbiol. Immunol., 2, 19-24, 1994; Kolenbrander et al., Meth. Enzymol., 253, 385-397, 1995; Hiroi et al., FEMS Microbiol Lett., 96, 193-198, 1992; Gibbons et al., Infect. Immun., 52, 555-561, 1986).

The organic acids produced by oral bacteria during the fermentation process directly cause dental caries. These acids attack the hard tissue of teeth with the consequent release of ions such as calcium, phosphate, carbonate, magnesium, fluoride, and sodium. When the pH in the oral cavity again increases to around neutrality, the saliva becomes saturated with calcium so that calcium liberation from the tooth is prevented. Among all the food residues found in the mouth, carbohydrates show the highest caries promoting effect since they are directly available for fermentation by oral bacteria.

Potentially all microorganisms that ferment sugars are cariogenic, but the primary etiological agents of coronal and root caries are the mutans streptococci because they are strong acid producers; Lactobacilli, that are highly aciduric, however, can also be implicated. In humans, *S. mutans* and S. *sobrinus* are the more cariogenic strains, and live on teeth while not colonizing the entire dentition. Their number is also less on anterior teeth than on molar teeth (Lindquist et al., Dent. Res., 69, 1160-1166, 1990). Moreover in human approximal plaque, *S. mutans* and *S. sobrinus* preferentially colonize the most caries-prone site apical to the contact area (Ahmady et al., Caries Res., 27, 135-139, 1993). A higher prevalence of S *sobrinus* was also found in the molar regions compared with that

of S. *mutans* (Lindquist et al., Caries Res., 25, 146-152, 1991).

S. mutans and *S. sobrinus* have been shown to attach to the pellicle of teeth mainly via specific adhesion-receptor interaction. Gibbons et al. showed that S *mutans* carries an adhesion which binds to salivary components in the pellicle, while *S. sobrinus* cells appear to possess an adhesion which binds to glucan in the pellicle (Infect. Immun., 52, 555-561, 1986).

The transient microflora comprise exogenous bacteria that are occasionally present in the mouth, but that do not establish a permanent residence therein (even if repeated oral administrations of these bacteria are carried out). All the food bacteria, and in particular lactic acid bacteria, can be part of this transient microflora. These exogenous lactic bacteria have never been shown to be capable of directly adhering to the pellicle of teeth. Repeated administration of exogenous lactic bacteria may, however, lead to colonization of the mouth on all the oral surfaces, such as the tongue, the buccal mucosa, the gingiva, lips, cheeks, palate, floor, and the teeth. This colonization may result from attachments via specific bindings to bacteria of the resident microflora (co-aggregation phenomena), via entrapment in the matrix of polysaccharide produced by the resident bacteria, or via adhesion to saliva proteins (especially glycoproteins).

Lactobacillus casei rhamnosus GG (ATCC53103) has been reported to colonize the mouth, most probably on the epithelium of the buccal mucosa. This strain also adheres to the epithelium of the intestinal tract (US Patent No. 5,032,399, Gorbach *et* al.; Micr. Ecol. In Health and Dis., 2, 295-298, 1994). By contrast *L. rhamnosus* does not adhere to teeth.

Japanese patent no. 4021633 (Cyconmedix KK) also reported colonization of the mouth by *Lactobacillus acidophilus*, most probably on the epithelium of the buccal mucosa. Many *Lactobacillus acidophilus* are known to also adhere to the epithelium of the intestinal tract (EP577904; EP199535; Perdigon et al., Medicina, 46, 751-754, 1986; Perdigon et al., Immunology, 63, 17-23, 1988).

Exogenous bacteria can also produce factors that inhibit the growth of the resident microflora in the mouth. For example, EP759469 (Société des Produits Nestlé) described the use of a bacteriocin produced by *Micrococcus varians* for inhibiting the development of the oral pathogens *S. sobrinus, S. sanguis, S. mutans,* and A. *viscosus.*

There are several strategies to minimize the development of resident microflora of the mouth. For example, by administering commensal bacteria of the resident

microflora that are not cariogenic, such as *Streptococcus salivarius* and/or Stomatococcus *mucilaginosus*, and/or repeated administration of exogenous lactic bacteria such as *L. casei, L. fermentum, L. acidophilus, L. crispatus, L. gasseri, L. salivarius, L bulgaricus*, and *S. salivarius* (Tanzer et al., Infec. and Immunity, 48,44-50, 1985; W092/14475).

The application of bacteriocins is another investigated strategy which has been used to reduce tooth caries. These molecules have attracted interest as prospective anti-carie agents and as factors important in modulating colonization of the oral cavity. The anti-carie potential of applying bacteriocins comes from their potent and broad antibacterial activity against mutans streptococci and bacteria associated with dental plaque and their natural occurrence in bacteria regarded as being safe to humans (US Patent No. 5,368,845 to Colgate, and WO 94/12150 to Smithkline Beecham).

The application of milk derivatives is also of interest for the health of the mouth. Indeed, US Patent No. 5,427,769 (Nestec S.A.) describes another alternative wherein dental caries are prevented by contacting teeth with an edible composition containing micellar casein in amount sufficient to inhibit colonization by *Streptococcus sobrinus*. EP748591 (Société des Produits Nestlé S.A.) also reports the use of fluoridated micellar casein or its micellar subunits for treating dental caries or plaque. US Patent No. 4,992,420 (Nestec S.A.) describes treatment of the buccal cavity with kappa-caseino-glycomacropeptide derived from milk for eradicating plaque and caries.

Lactic bacteria that are not part of the resident microflora of the mouth have never been shown to be really capable of directly adhering to the pellicle of teeth. By colonizing the surface of teeth, however, such lactic bacteria could exert an inhibitory activity against the growth of the resident microflora, including oral pathogens.

SUMMARY OF THE INVENTION

The present invention is directed to a method of treating or preventing dental caries, dental plaque, and periodontal infection in a humans or animals comprising administering to the oral cavity of a human or animal one or more lactic bacteria that are not part of the resident microflora of the mouth, that are low acidifying, and that are capable of adhering directly to the pellicle of the teeth to displace from the teeth or prevent attachment to the teeth of cariogenic strains of bacteria that are resident microflora of the mouth. In one embodiment the lactic bacteria to be administered provides a pH in the oral cavity of about 5.5 to 5.7. Advantageously, the lactic bacteria may be of dairy origin.

The lactic bacteria is preferably one or more of *Streptococcus thermophilus*, *Lactococcus lactis subsp. lactis*, or *Lactococcus lactis subsp. lactis biovar diacetylactis*. In particular the lactic bacteria is one of the strains CNCM I-1984, CNCM I-1985, CNCM I-1986, CNCM I-1987, and LMG P-18997.

Preferably, the lactic bacteria has optimal growth at a temperature of about 37°C, *i.e.*, the temperature of the mouth. The lactic bacteria may have been genetically modified to have improved adherence to the pellicle of the teeth or to be less acidifying than resident microflora found in the mouth. The lactic bacteria may be genetically modified to have improved adherence to the pellicle of the teeth by insertion of the X17390 gene, the X14490 gene, or the X53657 gene.

In another embodiment the method of the invention further involves administering the lactic bacteria in combination with one or more of milk, fermented milk, milk derivatives, or bacteriocin. The milk derivative may be one or more of a caseino-glycomacropeptide, micellar casein, fluorinated micellar casein, or renneted milk.

The invention also relates to dental compositions for use in the methods of the invention. The lactic bacteria may be present in these compositions in an amount of 10^4 to 10^9 cfu/g in order to provide a pH of at least 5.5 when the composition is administered to the mouth of a human or animal. When bacteriocin is present in an the composition, it is typically present in an mount of 0.00001 to 50 percent by weight of the composition. When the milk derivative is one or more of a caseino-glycomacropeptide, micellar casein, fluorinated micellar caesin, or renneted milk it may be present in an amount of at least about 0.1 percent by weight of the composition. The composition may further include one or more of an oil soluble antioxidant in an amount of about 0.005 to 0.5 percent by weight of the composition and an abrasive. The composition may be in the form of a toothpaste, mouth rinse, gum, spray, beverage, candy, infant formula, ice cream, frozen dessert, sweet salad dressing, milk preparation, cheese, quark, yogurt, acidified milk, coffee cream, or whipped cream.

The invention also relates to a method for screening lactic bacteria capable of adhering to teeth. The method involves the steps of preparing monoclonal antibodies that recognize specific surface proteins of lactic bacteria strains that are capable of adhering to the teeth and screening lactic bacteria strains with the monoclonal antibody to identify the strains of lactic bacteria that adhere to teeth.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 represents the adhesion saturation curves for *S. sobrinus* OMZ 176 (1a), *L. lactis* NCC2211 (1b), and *S. thermophilus* NCC1561 (1c);

Figure 2 represents the effect of CGMP on the adhesion to S-HA beads of *S. sobrinus* OMZ 176, *L. lactis* NCC2211, and *S. thermophilus* NCC1561;

Figure 3 represents the effect of As-CGMP on the adhesion to S-HA beads of *S. sobrinus* OMZ 176, *L. lactis* NCC2211, and *S. thermophilus* NCC1561.

DETAILED DESCRIPTION OF THE INVENTION

The object of the present invention is to use lactic bacteria that are not part of the resident microflora of the mouth, that is lactic bacteria that are low acidifying and that are capable of adhering directly to the pellicle of the teeth, to prepare a composition intended for the prophylaxis or the treatment of dental caries, dental plaque, and periodontal infection.

In one embodiment of the invention the lactic bacteria have been genetically modified to increase its adherence to the pellicle of the teeth via adhesion factors and/or genetically modified to be even less acidifying, contributing to a pH in the oral cavity of about 5.5 to 7.

The lactic bacteria may be selected from the group consisting of:

- an acidifying lactic bacteria that adheres to the pellicle of the teeth and that has been genetically modified so that it is low acidifying compared to resident microflora;
- a non adherent lactic bacteria that is low acidifying and that has been genetically modified so that it adheres to the pellicle of the teeth;
- a non-adherent acidifying lactic bacteria that has been genetically modified so that it adheres to the pellicle of the teeth and genetically modified so that it is low acidifying compared to resident microflora.

In another embodiment the bacteria, that is not part of the resident microflora, is low acidifying compared to resident microflora and is capable of adhering directly to the pellicle of the teeth.

In another embodiment the composition for the health of the mouth comprises (1) at least a lactic bacteria that is not part of the resident microflora of the mouth, which is capable of adhering directly to the pellicle of the teeth and contributing to a

pH in the oral cavity of above 5.5, and (2) any form of caseinoglycomacropeptide, micellar casein, fluorinated micellar casein, renneted milk, or bacteriocin.

The invention also provides a method for screening lactic bacteria capable of adhering to tooth. The method comprises the steps of: (1) preparing monoclonal antibody recognizing specific surface proteins of a lactic bacteria strain capable of adhering to the teeth, and (2) screening any lactic bacteria strain by use of the monoclonal antibody of strain capable of adhering to the teeth.

The term "mouth," as used herein defines the oral cavity of humans or animals such as pets, composed by the oral mucosa (gums, lips, cheeks, palate, and floor of the mouth), the tongue, and the teeth (including artificial structures).

Resident microflora of the mouth includes all microorganisms that naturally live in the mouth because they can establish a permanent residence on the oral surfaces. The resident microflora of the mouth also includes bacteria that live in the interfacial region between the dental hard and soft tissues (the junction tooth-gingiva), even thought the gingival crevice and the periodontal pocket are not present in a healthy mouth. This microflora includes microorganisms selected from *Streptococcus, Staphylococcus, Enterococcus, Micrococcus, Peptostreptococcus, Peptococcus, Lactobacillus, Corynebacterium, Actinomyces, Arachnia, Rothia, Alcaligenes, Eubacterium, Propionibacterium, Bifidobacterium, Bacillus, Clostridium, Neisseria/Branhamella, Veillonella, Enterobacteriaceae, Campylobacter, Eikenella, Actinobacillus, Capnocytophga, Haemophilus, Simonsiella, Bacteroides, Fusobacterium, Porphyromonas, Prevotella, Leptotrichia, Wohlinella/Selenomonas, Mycoplasma, Candida, Spirochaetes,* Protozoa.

Transient microflora comprises exogenous bacteria that can be occasionally present in the mouth, but that do not establish a permanent residence. This transient microflora may comprise all the food micro-organisms, such as the bifidobacteria *(B. infantis, B. adolescentis, B. breve* and *B. longum);* the lactococci *(Lactococcus lactis* subsp. *lactis, Lactococcus lactis* subsp. *cremoris,* and *Lactococcus lactis* subsp. *lactic biovar diacetylactis);* the streptococci *(Streptococcus thermophilus, S. lactis, S. lactis cremoris* and S. *lactis diacetylactis);* the Lactobacilli *(Lactobacillus delbrueckii* subsp. *bulgaricus, Lactobacillus helveticus, Lactobacillus farciminis, Lactobacillus alimentarius, Lactobacillus casei* subsp. *casei, Lactobacillus delbruckii* subsp. *lactis, Lactobacillus sake, Lactobacillus curvatus, Lactobacillus fermentum*; and the acidophile group comprising *L.*

johnsonii; (see Fujisawa et al., Int. J. Syst. Bact., 42, 487-491, 1992); the pediococci *(Pediococcus pentosaceus, Pediococcus acidilactici,* and *Pediococcus halophilus);* the enterococci; the staphilococci *(Staphylococcus xylosus* and *Staphylococcus carnosus);* the micrococci *(Micrococcus varians);* yeast of the genus *Debaromyces, Candida, Pichia, Torulopsis* and *Saccharomyces;* and mold of the genus *Aspergillus, Rhizopus, Mucor* and *Penicillium.*

The lactic bacteria according to the invention that are low acidifying and capable of adhering directly to the pellicle of the teeth that are used to prepare compositions for the prophylaxis or the treatment of dental caries, dental plaque, and periodontal infection displace pathogenic bacteria from the teeth or prevent the attachment of the pathogenic bacteria. The lactic bacteria according to the invention are "low acidifying," which means that they are less acidifying than pathogenic strains. Accordingly, they contribute to a pH in the oral cavity of about 5.5 to 7. Preferably, they are from dairy origin.

The lactic bacteria according to the invention adhere to the pellicle of the teeth via specific or unspecific interactions and/or adhesion factors. The specific adhesion factors are proteins or polysaccharides.

At least one lactic bacteria is selected from the group consisting of *Streptococcus thermophilus, Lactococcus lactis subsp. lactis,* and *Lactococcus lactis subsp. Lactis biovar diacetylactis* and particularly from the group consisting of the strains CNCM 1-1984, CNCM 1-1985, CNCM 1-1986, CNCM 1-1987, and LMG P-18997. These strains have been selected among lactic bacteria strains for their capacity to adhere to the pellicle of the teeth and their optimal growth temperature of about 37°C, which is the temperature in the oral cavity. Moreover they are capable of fermenting glucose and sucrose and do not synthesize glucans, which are factors leading to the pathogenicity of the cariogenic strains.

In one embodiment of the invention the lactic bacteria are genetically modifying so that they adhere to the pellicle of the teeth via adhesion factors. For lactic bacteria that already adhere to the pellicle of the teeth, this modification makes the strains more adherent to the surface of the teeth. In the same way, any non-adherent lactic acid bacteria (not Lactobacilli) can be genetically modified so that it adheres to the pellicle of the teeth. This modification of the lactic bacteria can be achieved, for example, by insertion of the genes X17390, X14490 or X53657 (GenBank accession numbers). These gene are responsible in S. *mutans* for the expression of the Antigen I/II that mediates adhesion to salivary glycoproteins.

According to the invention, it is also possible to genetically modify lactic bacteria so that they are low acidifying. For lactic bacteria that is already low acidifying this modification increases the effect by further decreasing lactic acid production. This modification can be achieved in many ways. Preferably, the modification is achieved according to one the protocols described in the following documents: Boumerdassi et al., Appl. Environ. Microbiol., 63, 2293-2299, 1997; Plattecuw et al., Appl. Environ. Microbiol, 61, 3967-3971, 1995; Ito et al., Biosci. Biotechnol. Biochem., 58, 1569-1573, 1994.

According to the invention, at least one lactic bacteria, genetically modified or not, is used in an "effective amount" for the preparation of compositions intended for the prophylaxis or the treatment of dental caries, dental plaque, and periodontal infection in humans or animals such as pets. This quantity is preferably between 10^4 to 10^9 cfu/g.

It is also possible to use the at least one lactic bacteria, in combination with milk derivatives, such as milk, fermented milk, or milk derivatives selected from any forms of caseino-glycomacropeptide, micellar casein, fluorinated micellar casein, renneted milk, or bacteriocin, for example.

Biochemical Characterization of the Selected Strains

Fermentation patterns: 49 simple sugars were tested with the api 50 CH bioMerieux strip test (bioM6rieux SA, 69280 Marcy-l'Etoile, France). The results are given in the Table 1.

Acidification curves: Acidification curves were determined at 37°C under the following conditions:

- *S. sobrinus* OMZ 176: FUM sucrose 1% and FUM glucose 1%
- *S. thermophilus* CNCM 1-1985: Belliker sucrose 1% and Belliker glucose 1%

Inoculation was always 5%. The pH was recorded every 20 min.

S..*thermophilus* CNCM 1-1985, from sucrose fermentation, lowers the pH to 4.5, while *S. sobrinus* OMZ 176 lowers the pH to 4.

Table I. Sugar fermentation of *L. lactis* CNCM I- 1987, *L. lactis* CNCM I-1986, *S. thermophilus* CNCM I-1984, S. *thermophilus* CNCM I-1985 and , *S. thermophilus* LMG P-18997.

Sugar	*L. lactis* CNCM I-1987	*L. lactis* CNCM I-1986	*S. th.* CNCM I-1984	*S. th.* CNCM I-1985	*S. th.* LMG P-18997
Adonitol	+++				
Aesculin	++	++++			
Amygdalin	++++				
D-Arabinose					
L-Arabinose					
D-Arabitol					
L-Arabitol	+++				
Arbutin	+++	+++			
Cellobiose	+++	+++			
Dulcitol					
Erythritol					
D-Fructose	+	++++			
D-Fucose					
L-Fucose					
Galactose	++	++++			
β-Gentiobiose		+++			
Gluconate					
2-keto-Gluconate					
5-keto-Gluconate					
GlcNAc	+	++++			
D-Glucose	+	++++	+	++	++
Glycerol					
Glycogen					
Inositol					
Inulin					
Lactose	+	++++	+++	++++	++++
D-Lyxose					
Maltose	++				
Mannitol	+++	++			

D-Mannose	+	++++			
Melezitose					
Melibiose					
α-Methyl-D-glucoside					
α-Methyl-D-mannoside					
D-Raffinose					
Rhamnose					
Ribose	++	++			
Salicin	+++	+++			
Sorbitol					
L-Sorbose					
Starch					
Sucrose			+++	++++	+++
D-Tagatose					
Trehalose	++				
D-Turanose	++				
Xylitol	+++				
D-Xylose					
L-Xylose					
β-methil-xyloside					

+, ++, +++, ++++ show if the fermentation begins after 3, 6, 24, or 48 hours, respectively.

The invention is also directed to compositions for the health of the mouth that comprise a lactic bacteria that is not part of the resident microflora of the mouth, that is low acidifying, and that is capable of adhering directly to the pellicle of the teeth. The compositions are particularly intended for the prophylaxis or the treatment of dental caries, dental plaque, and periodontal infection. The lactic bacteria strain may be selected from the group consisting of *Streptococcus thermophilus*, *Lactococcus lactis subsp. lactis*, and *Lactococcus lactis subsp. lactis biovar diacetylactis* and preferably from the group consisting of the strains CNCM I-1984, CNCM I-1985, LMG P-18997, CNCM I-1986, and CNCM I-1987. In these compositions the lactic bacteria strains may be genetically modified as described above.

The lactic bacteria strains may be included in a food, pet food, cosmetic, or

pharmaceutical composition, for example. Accordingly, the compositions are preferably a toothpaste, mouth rinse, gum, spray, beverage, candy, infant formula, ice cream, frozen dessert, sweet salad dressing, milk preparation, cheese, quark, yogurt, acidified milk, coffee cream, or whipped cream, for example.

In the compositions of the invention, the lactic bacteria strains may be included alone or in combination with milk derivatives, for example, in order to obtain synergistic preparations. Accordingly, these compositions for the health of the mouth comprise:

- a lactic bacteria that is not part of the resident microflora of the mouth, which is capable of adhering directly to the pellicle of the teeth;
- any forms of lactic glycopeptides, renneted milk, or bacteriocin.

The lactic glycopeptides are preferably caseino-glycomacropeptides (CGMP), fluorinated or non-fluorinated micellar casein (which can be obtained as described in EP 0 604 802 and EP 0 748 591), or renneted milk.. The caseino-glycomacropeptides are preferably added in a minimum amount of about 0.1%. It has also been shown that the caseino-glycomacropeptides do not prevent the lactic bacteria from adhering to the teeth pellicle (Fig. 2 and 3).

Synergistic compositions may also be prepared by adding at least one bacteriocin which is active against Gram-positive oral bacteria. In this embodiment the oral hygiene compositions may comprise 0.00001 to 50%, and preferably from 0.00001 to 15% of purified bacteriocin, by weight of the composition. The bacteriocin is preferably variacin (EP 0759469).

To protect the composition from degradation, an oil-soluble antioxidant may also be included. Suitable antioxidants include the "tocopherols," butyl-hydroxyanisole (BHA), butyl-hydroxytoluene (BHT), and ascorbyl palmitate. The oil soluble antioxidant is present in amounts of from 0.005% to 0.5%, preferably 0.005% to 0.01% by weight of the composition.

Suitable abrasives for use in dentifrice compositions of the present invention include calcium carbonate, calcium aluminosilicate, alumina hydrates, alumina, zinc orthophosphate, plastic particles, and silica, of which silica is the preferred abrasive.

Compositions according to the invention will have a pH which is orally acceptable and within a range such that the activity of the lactic bacteria is not compromised. The pH may be in the range of 3.0 to 9.5, preferably in the range 3.5 to 6.5.

The compositions of the invention may be prepared by conventional processes that comprise admixing the ingredients together in the appropriate relative amounts and finally, if necessary, adjusting the pH to the desired value.

The invention is further directed to a method for screening lactic bacteria capable of adhering to tooth. This method comprises the steps of:

(1) preparing monoclonal antibodies that recognize specific surface proteins of a lactic bacteria strain capable of adhering to the teeth, and

(2) screening any lactic bacteria strain by using the monoclonal antibody of strain capable of adhering to the teeth.

The monoclonal antibodies are used as a tool to detect the said lactic bacteria strain among other strains growing nearby.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention, in addition to those described herein, will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the claims. Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties to the extent necessary for understanding the present invention. DNA manipulation, cloning and transformation of bacteria cells are, except where otherwise stated, carried out according to the textbook of Sambrook et al. (Sambrook et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press, U.S.A., 1989).

EXAMPLES

The examples are preceded by a brief description of the plasmids, strains, and the various media used, as well as the method for producing a monoclonal antibody.

The strains S. *thermophilus* S118 (NCC 1529), S123 (NCC 1561), *L. lactis subsp. Lactis* 29 (NCC 2211), *L. lactis subsp. lactis biovar dioacetylactis* 69 (NCC 2225) were deposited under the Budapest Treaty at the Collection Nationale de Culture de Microorganismes (CNCM 1-1984, CNCM 1-1985, CNCM 1-1986 and CNCM 1-1987, respectively), 25 rue du docteur Roux, 75724 Paris, France, on March 3rd, 1998. The strain *S. thermophilus* BF1 1116 (CNBL 1177) was deposited under the Budapest Treaty at the Belgian Coordinated Collections of Microorganisms LMG P-18997, K.L. Ledeganckstraat 35, B-9000 Gent, Belgium, on July 5th, 1999. All restrictions as to the availability of these

deposits will be withdrawn upon first publication of this application or another application which claims benefit of priority to this application.

Example 1: Strains and Culture Conditions

More than 100 strains (belonging to the Nestlé culture collection) were screened for their ability to attach to saliva-coated hydroxyapatite beads, and in particular the following 23 strains: *S. thermophilus* Y54 (NCC 2284), *S. thermophilus* 5fi6 (NCC 1971), *S. thermophilus* Sfi13 (NCC 2008), *S. thermophilus* Sfi21 (NCC 2038), *S. thermophilus* Sfi39 (NCC 2130), *S. thermophilus* Sfi42 (NCC 2145), *S. thermophilus* Sfi47 (NCC 2172), *S. thermophilus* S118 (NCC 1529), *S. thermophilus* S119 (NCC 1536), *S. thermophilus* S122 (NCC 1554), *S. thermophilus* S123 (NCC 1561), *S. thermophilus* S126 (NCC *1587), L. lactis subsp. cremoris* 15 (NCC 92), *L. lactis subsp. cremoris* 25 (NCC 1932), *L. lactis subsp. cremoris* 136 (NCC 2419), *L. lactis subsp. diacetylactis* 8 (NCC 1970), *L. lactis subsp. diacetylactis* 28 (NCC 2057), *L. lactis subsp. diacetylactis* 69 (NCC 2225), *L. lactis subsp. diacetylactis* 80 (NCC 2272), *L. lactis subsp. lactis* 29 (NCC 2211), *L. lactis subsp. lactis* 50 (NCC 2224), *L. lactis subsp. lactis* 54 (NCC 2228), *S. macedonicus* 216 (NCC 2484).

The 5 oral strains, *S. sobrinus* OMZ 176, S. *oralis* OMZ 607, *A. naeslundii* OMZ 745, *V. dispar* OMZ 493 and *F. nucleatum* OMZ 596 were obtained from the Institute für Orale Mikrobiologie und Aligemeine Immunologie, University of Zürich and were cultured in FUM medium in anaerobiosis (GasPackSystem, BBL) at 37°C.

All the strains were stored in glycerol at -20°C and pre-cultured for 14 hours prior to use at their specific optimal temperature; *S. sobrinus* OMZ 176 grew in FUM medium lactococci and streptococci in M17 (Difco) except S. *thermophilus* NCC1529, S119, S122, NCC1561 and S126 that grew in Belliker (prepared by dissolution of 20 g tryptone, 5 g yeast extract, 2.5 g gelatine, 5 g dextrose, 5 g sucrose, 5 g lactose, 4 g NaCl, 0.5 g Ascorbic acid, and 10 g beef extract in 1 L of water).

For plate counting, S. *sobrinus* OMZ 176 was cultured in Mitis-Salivarius agar (Difco), S. *thermophilus* NCC1529, S119, S122, NCC1561, BF11116, and S126 in Belliker agar (prepared by adding to liquid Belliker 15 g of Bacto agar, Difco), and the remaining lactic bacteria strains in M17 agar (Oxoid).

Example 2: Production of Monoclonal Antibody

A monoclonal antibody would be used as a tool to detect *L. lactis subsp. lactis* NCC2211 among 5 oral strains growing together on S-HA discs and forming a biofilm that simulates dental plaque. Therefore the monoclonal antibody was tested against these strains to verify there was no cross-reaction. To this end, the monoclonal antibody is produced as described by Granato et al. "A mouse monoclonal IgE antibody anti-bovine milk lactoglobulin allows studies of allergy in the gastrointestinal tract., Clin. Exp. Immunol., 63, 703-710, 1986.

Example 3: Selection of Adherent Lactic Bacteria

Attachment to saliva-coated hydroxyapatite beads (S-HA)

To select among the lactic bacteria dairy strains those strains that are able to attach to saliva-coated hydroxyapatite beads (S-HA), the procedure previously described by Neeser et al. (1994) was used with slight modification in that the bead washings were done with 150 µl volumes and Hyamine hydroxide was substituted with Benzethonium hydroxide (Sigma).

Briefly, all the strains were grown to the end of the log phase in FUM except *S. thermophilus* NCC1529, S119, S122, NCC1561, and S126 that were cultured in Belliker. S. *sobrinus* OMZ 176, *L. lactis subsp. lactis* NCC221 1, 50 and 54, *S. thermophilus* NCC1529, S119, S122, NCC1561, and S126 grew at 37°C, the remaining lactococci at 30°C, and the remaining streptococci at 42°C.

5 mg of hydroxyapatite beads (BDH Chemicals Ltd, Poole, England) were covered with 70 µl clarified saliva obtained from volunteers in the lab and prepared as previously explained (Neeser et al, 1994). Saliva coated beads were kept overnight at 4°C, then washed (first with distilled water and after with HEPES buffer) and finally inoculated with 100 µl of metabolically labeled bacterial suspension (bacteria had been grown in medium supplemented with 10 µCi/ml ^{14}C acetic acid). Adhesion took place during 45 min at 37°C, then unbound bacteria were washed away and the attached cells directly counted in a LKB scintillation counter (type 1219 Rackbeta).

Adhesion percentages are expressed as radioactivity bound to the beads relative to the total radioactivity added to each well. All measurements were done in triplicate. Table 2 reports the percentages of adhesion to saliva-coated hydroxyapatite beads obtained for several screened strains and for *S. sobrinus* OMZ 176 (the reference strain).

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Briefly, all the strains were grown to the end of the log phase in FUM except *S. thermophilus* NCC1529, S119, S122, NCC1561, and S126 that were cultured in Belliker. S. *sobrinus* OMZ 176, *L. lactis subsp. lactis* NCC221 1, 50 and 54, *S. thermophilus* NCC1529, S119, S122, NCC156l, and S126 grew at 37°C, the remaining lactococci at 30°C, and the remaining streptococci at 42°C.

5 mg of hydroxyapatite beads (BDH Chemicals Ltd, Poole, England) were covered with 70 µl clarified saliva obtained from volunteers in the lab and prepared as previously explained (Neeser et al, 1994). Saliva coated beads were kept overnight at 4°C, then washed (first with distilled water and after with HEPES buffer) and finally inoculated with 100 µl of metabolically labeled bacterial suspension (bacteria had been grown in medium supplemented with 10 µCi/ml ^{14}C acetic acid). Adhesion took place during 45 min at 37°C, then unbound bacteria were washed away and the attached cells directly counted in a LKB scintillation counter (type 1219 Rackbeta).

Adhesion percentages are expressed as radioactivity bound to the beads relative to the total radioactivity added to each well. All measurements were done in triplicate. Table 2 reports the percentages of adhesion to saliva-coated hydroxyapatite beads obtained for several screened strains and for *S. sobrinus* OMZ 176 (the reference strain).

Table 2: Percentages of Adhesion to Saliva-coated Hydroxyapatite Beads for Several Screened Strains.

STRAIN	% ADHESION (± SD)
***S. sobrinus* OMZ 176**	**2.23 ± 0.49**
S. thermophilus Sfi42 (NCC 2145)	0.08 ± 0.02
S. thermophilus Sfi47 (NCC 2172)	0.14 ± 0.04
S. thermophilus NCC1529	**2.89 ± 0.60**
S. thermophilus S119 (NCC 1536)	0.15 ± 0.04
S. thermophilus S122 (NCC 1554)	0.93 ± 0.17
***S. thermophilus* NCC1561**	**2.19 ± 0.50**
S. thermophilus S126 (NCC 1587)	1.19 ± 0.56
L. lactis subsp. diacetylactis 28 (NCC 2057)	1.59 ± 0.17
***L lactis subsp. diacetylactis* NCC2225**	**1.96 ± 0.40**
L. lactis subsp. diacetylactis 80 (NCC 2272)	1.20 ± 0.35
***L lactis subsp. lactis* NCC2211**	**2.85 ± 0.85**

Four strains, *S. thermophilus* NCC 1529 (CNCM 1-1984), *S. thermophilus* NCC1561 (CNCM 1-1985), *L. lactis subsp. lactis* NCC2211 (CNCM 1-1986) (hereinafter *L. lactis* NCC2211) and *L. lactis subsp. diacetylactis* NCC2225 (CNCM 1-1987) showed adhesion values close to *S. sobrinus* OMZ 176.

L. lactis NCC2211 and *S. thermophilus* NCC1561 were chosen as the more promising candidates since they grow very well at 37°C, which is the temperature in the mouth, while *L. diacetylactis* NCC2225 has an optimal growth temperature of 30°C. In particular, *L. lactis* NCC2211 cannot grow on sucrose, but it can ferment a wide range of sugars, moreover other oral strain can provide glucose via their invertase.

Adhesion saturation curves

Curves of bound CFU versus CFU inoculated into the well were determined to verify if bead saturation could be obtained. The 50% saturation was obtained directly from the bending point of the curves. The adhesion saturation curves for *S. sobrinus* OMZ 176, *L. lactis* NCC2211, and *S. thermophilus* NCC 1561 were determined. They are shown in Figure 1.

For each of the three strains the CFU number inoculated in the well to get

50% bead saturation and the corresponding number of bound CFU were directly deduced from the bending point of the curves and are given in the table 3.

Table 3: Number of CPU Inoculated Per Well to get 50% Bead Saturation.

	cfu/well	Bound cfu	% adhesion
S. sobrinus OMZ 176	4.00 E+07	4.00 E+06	10%
L. lactis NCC2211	1.00 E+07	9.00 E-f-05	9%
S. thermophilus NCC156I	3.00 E+07	2.00 E+06	7%

Example 4: Effect of Caseino-glycomacropeptides

The influence of CGMP on the adhesion of *L. lactis* NCC2211 and *S. thermophilus* NCC1561 was studied to verify the possibility of using CGMP to foster the predominance of one of these two strains over pathogenic strains, namely *S. Sobrinus OMZ* 176. Caseino-glycopeptide (CGMP) and its desialylated derivative (As-CGMP) were obtained from Nestec S. A., Lausanne (for their preparation see Neeser et al., 1994).

The dose-response effect was studied on the adhesion to S-HA beads by inoculating, in the well, 100 µl of bacterial suspension (CFU/ml corresponding to the 50% bead saturation previously calculated) which contained CGMP or AsCGMP in different concentrations and then performing the adhesion assay in the usual manner. Concentrations in the range 0.05 to 3 mg/ml were tested. No previous incubation of the bacteria in presence of CGMP or As-CGMP was done.

Figure 2 provides the curves obtained for the three strains by plotting the number of bound cells versus increasing amounts of CGMP, the number of inoculated cells corresponds to 50% bead saturation formerly calculated for each strain. The strong inhibition observed in the case of S. *sobrinus* OMZ 176 confirms the previous results obtained by Neeser et al. (1994) and Schupbach et al. (J. Dent. Res., 75, 1779-1788, 1996).

Figure 2 shows that 0.25 mg/ml produced 50% inhibition of the adhesion of *S. sobrinus* OMZ 176, while more than 2 mg/ml were necessary to have the same effect with *S. thermophilus* NCC156I. CGMP slightly enhances the adhesion of L. *lactis* NCC2211.

As in the case of CGMP, the desyalilated derivative inhibits the adhesi n of *S. sobrinus* OMZ 176; only 0.05 mg/ml are needed to produce 50% decrease in the adhesion percentage. As-CGMP does not influence *L. lactis* NCC2211 adhesion, while it slightly

fosters the adhesion of *S. thermophilus* NCC1561 (Fig. 3).

Example 5: Toothpaste

Toothpaste is prepared by adding 10^5 cfu/ml of at least one of the lactic bacteria strain CNCM 1-1984, CNCM 1-1985, CNCM 1-1986, CNCM 1-1987 or LMG P-18997 in a lyophilized form, to a mixture containing:

Cetyl pyridinum chloride	1.65%
Sorbitol (70% soln)	33.0%
Glycerin	25.0%
Sodium carboxymethyl cellulose	2.0%
Sodium fluoride	0.25%
Silica (RP 93)	26.3%
Thickening Silica (Sident 22)	8.1%
Sodium saccharine	0.5%
Poloxamer (Pluronic F 108)	3.2%

The toothpaste is intended for the prophylaxis or the treatment of dental caries, dental plaque, and periodontal infection.

Example 6: Ice Cream

A cream comprising 10.8% lactic fats, 13.5% milk solids (non fat), 0.3% Emulstab® SE30 and 0.3% Emulstab® foam (Grindsted, DK) is prepared and then pasteurized at 105°C for 20s, homogenized at 75°C and 300 bar, cooled to 38°C, and inoculated with pre-cultures in MRS medium, taken in the exponential growth phase, at a rate of 10^7 to 10^8 cfu/ml of at least one of the lactic bacteria strain of CNCM 1-1984, CNCM 1-1985, CNCM 1-1986, CNCM 1-1987 or LMG P-18997. The cream is then fermented for 10 hours at 38°C up to a pH of about 4.5. At the end of the fermentation, sucrose and glucose syrup is added thereto. The composition of the cream is presented in table 4 below. The mixture is then beaten, cooled to 4°C, stored at 4°C, and chilled to a degree of expansion of 95°C by volume.

Table 4: Ice Cream Composition

Ingredients	Composition (kg)	Fats (%)	Non-fat solids (%)	Sucrose (%)	Solids content (%)
Cream (35%)	30.83	10.79	1.54		12.33
Powdered skimmed milk	12.45		11.95		11.95
Emulstab® 5E30	0.41				0.37
Emulstab® foam	0.41				0.36
Water	55.91				
Total: cream base	100.00	10.79	13.49	-	25.01
Cream base	74.14	8.00	10.00	-	18.54
Sucrose	22.06			15.00	15.00
Glucose syrup	3.80				3.00
Fermented Ice cream	100.00	8.00	10.00	15.00	36.54

Example 7: Yogurt

5 L MRS culture medium were sterilized for 15 min at 121 °C and then inoculated with 5% by volume of an active culture of at least one of the *S. Thermophilus* strains CNCM 1-1984, CNCM 1-1985, or LMG P-18997 containing approximately 10^9 cfu/ml. After incubation for 8 h at 41 °C, a starter containing 4.5×10^8 cfu/ml was obtained.

5 L of reconstituted skimmed milk having a dry matter content of 10%, to which 0.1% yeast extract had been added, was sterilized for 15 min at 121 °C and inoculated with 2% of an active culture of commercial thickening *Streptococcus thermophilus* containing approximately 10^9 cells/ml. After incubation for 4 h at 41 °C, a starter containing 4.5×10^8 cells/ml was obtained.

One batch of whole milk containing 3.7% fats strengthened with 2.5% skimmed milk powder and then pasteurized for 30 min at 90°C was then inoculated with 2% by volume of the starter of at least one of the CNCM 1-1984, CNCM 1-1985 or LMG P-18997 strains and 3% by volume of the starter of thickening *Streptococcus thermophilus*. The inoculated milk is stirred, poured into pots, and incubated for 4 h at 41 °C. The resulting yogurt obtained has a good firm and smooth texture and is intended for the health of the mouth.

Example 8: Chewing Gum

A chewing gum for preventing or treating dental caries, dental plaque, or periodontal infection can be prepared adding an active culture of at least one of the *S. Thermophilus* strains CNCM 1-1984, CNCM 1-1985, or LMG P-18997 so that it contains approximately 10^4 to 10^9 cfu/g, to the following typical ingredients:

Xylitol	67.5 %
Gum base	20%
Calcium carbonate	5 %
Glycerin	3 %
PluronicFl27	2%
Cellulose gum	1 %
Ballast compounds	0.5%
Flavor	1 %

Example 9: Pet Food Composition

A pet food for mouth health is obtained by preparing a feed mixture made up of corn, corn gluten, chicken and fish meal, salts, vitamins, and minerals. The feed mixture is fed into a pre-conditioner and moistened. The moistened feed leaving the pre-conditioner is then fed into an extruder-cooker and gelatinised. The gelatinised matrix leaving the extruder is forced through a die and extruded. The extrudate is cut into pieces suitable for feeding to dogs, dried at about 110°C for about 20 minutes, and cooled to form pellets which have a water activity of about 0.6. The pellets are sprayed with 3 coating mixtures. Each coating mixture contains an active culture of at least one of the *S. Thermophilus* strains CNCM 1-1984, CNCM 1-1985, or LMG P-18997 but one coating mixture uses hydrogenated soy fat as a coating substrate, one coating mixture uses water as a coating substrate, and one coating mixture uses protein digest as a coating substrate. The pellets contain approximately 10^4 to 10^9 cfu/g of the strains.

The Claims

What is claimed is:

1. A method of treating or preventing dental caries, dental plaque, and periodontal infection in a humans or animals comprising administering to the oral cavity of a human or animal one or more lactic bacteria that are not part of the resident microflora of the mouth, that are low acidifying, and that are capable of adhering directly to the pellicle of the teeth to displace from the teeth or prevent attachment to the teeth of cariogenic strains of bacteria that are resident microflora of the mouth.

2. The method of claim 1, wherein the lactic bacteria to be administered provides a pH in the oral cavity of about 5.5 to 5.7.

3. The method of claim 1, wherein the lactic bacteria are of dairy origin.

4. The method of claim 1, wherein the lactic bacteria comprise one or more of *Streptococcus thermophilus*, *Lactococcus lactis subsp. lactis*, or *Lactococcus lactis subsp. lactis biovar diacetylactis*.

5. The method of claim 1, wherein the lactic bacteria are one or more of the strains CNCM I-1984, CNCM I-1985, CNCM I-1986, CNCM I-1987, or LMG P-18997.

6. The method of claim 1, wherein the lactic bacteria have optimal growth at a temperature of about 37°C.

7. The method of claim 1, wherein the lactic bacteria have been genetically modified to have improved adherence to the pellicle of the teeth or to be less acidifying than the resident microflora in the mouth.

8. The method of claim 7, wherein the lactic bacteria have been genetically modified to have improved adherence to the pellicle of the teeth by insertion of the X17390 gene, the X14490 gene, or the X53657 gene.

9. The method of claim 1, further comprising administering the lactic bacteria in combination with one or more of milk , fermented milk, milk derivatives, or bacteriocin.

10. The method of claim 9, wherein the milk derivative comprises one or more of a caseino-glycomacropeptide, micellar casein, fluorinated micellar caesin, or renneted milk.

11. A composition for preventing dental caries, dental plaque, and periodontal infection comprising one or more lactic bacteria that are not part of the resident microflora of the mouth selected from the group consisting essentially of acidifying lactic bacteria that adhere to the pellicle of the teeth that have been genetically modified to be low acidifying compared to resident microflora, low acidifying lactic bacteria that does not adhere to the pellicle of the teeth that has been genetically modified to adhere to the pellicle of the teeth, acidifying lactic bacteria that does not adhere to the pellicle of the teeth that has been genetically modified to be low acidifying compared to resident microflora and to adhere to the pellicle of the teeth, and mixtures thereof.

12. The composition of claim 11, wherein the lactic bacteria is present in an amount of 10^4 to 10^9 cfu/g in order to provide a pH of at least 5.5 when the composition is administered to the mouth of a human or animal..

13. The composition of claim 11, wherein the lactic bacteria one or more of *Streptococcus thermophilus*, *Lactococcus lactis subsp. lactis*, or *Lactococcus lactis subsp. lactis biovar diacetylactis*.

14. The composition of claim 11, wherein the lactic bacteria are selected from the strains CNCM I-1984, CNCM I-1985, CNCM I-1986, CNCM I-1987, and LMG P-18997.

15. The composition of claim 11, wherein the lactic bacteria have optimal growth at a temperature of about 37°C.

16. The composition of claim 11, wherein the lactic bacteria have been genetically modified to have improved adherence to the pellicle of the teeth by insertion of the X17390 gene, the X14490 gene, or the X53657 gene.

17. The composition of claim 11, further comprising one or more of milk, fermented milk, milk derivatives, or bacteriocin.

18. The composition of claim 17, wherein the bacteriocin is present in an mount of 0.00001 to 50 percent by weight of the composition.

19. The composition of claim 17,wherein the milk derivative comprises one or more of a caseino-glycomacropeptide, micellar casein, fluorinated micellar casein, or renneted milk in an amount of at least about 0.1 percent by weight of the composition.

20. The composition of claim 11, further comprising one or more of an oil soluble antioxidant in an amount of about 0.005 to 0.5 percent by weight of the composition and an abrasive.

21. The composition of claim 11, in the form of a toothpaste, mouth rinse, gum, spray, beverage, candy, infant formula, ice cream, frozen dessert, sweet salad dressing, milk preparation, cheese, quark, yogurt, acidified milk, coffee cream, or whipped cream.

22. A method for screening lactic bacteria capable of adhering to teeth comprising:

preparing monoclonal antibodies that recognize specific surface proteins of lactic bacteria strains that are capable of adhering to the teeth; and

screening lactic bacteria strains with the monoclonal antibody to identify the strains of lactic bacteria that adhere to teeth.

INCORPORATION OF EXOGENOUS LACTIC BACTERIA INTO ORAL MICROFLORA

ABSTRACT

Compositions for the prophylaxis or treatment of dental caries, dental plaque, and periodontal infection that include lactic bacteria that are not part of the resident microflora of the mouth, that are low acidifying, and that are capable of adhering directly to the pellicle of the teeth. The compositions are used in methods of treating or preventing dental caries, dental plaque, and periodontal infection.

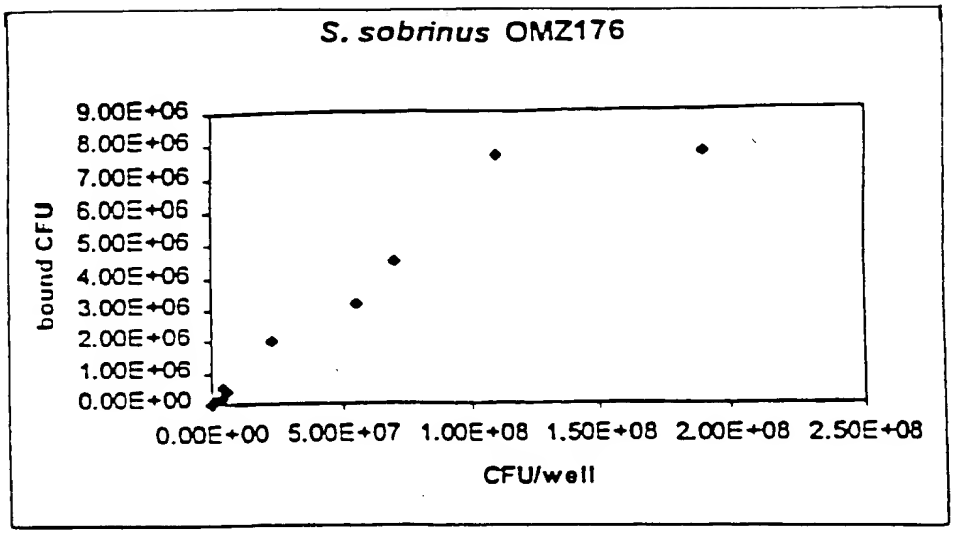


Figure 1a

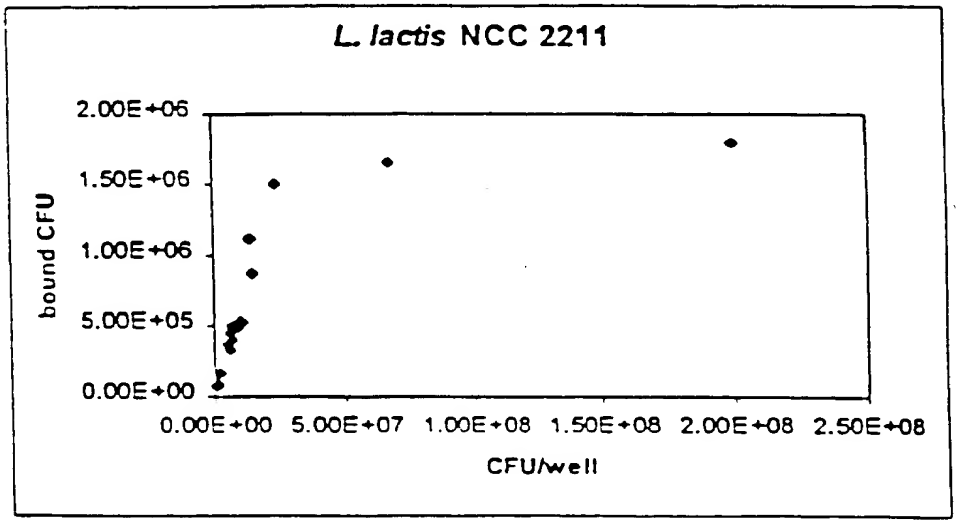
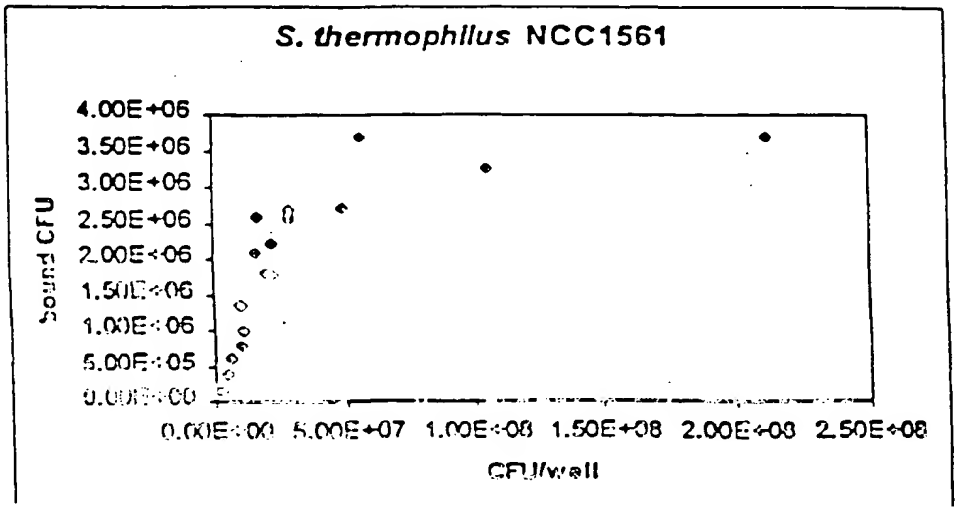


Figure 1b



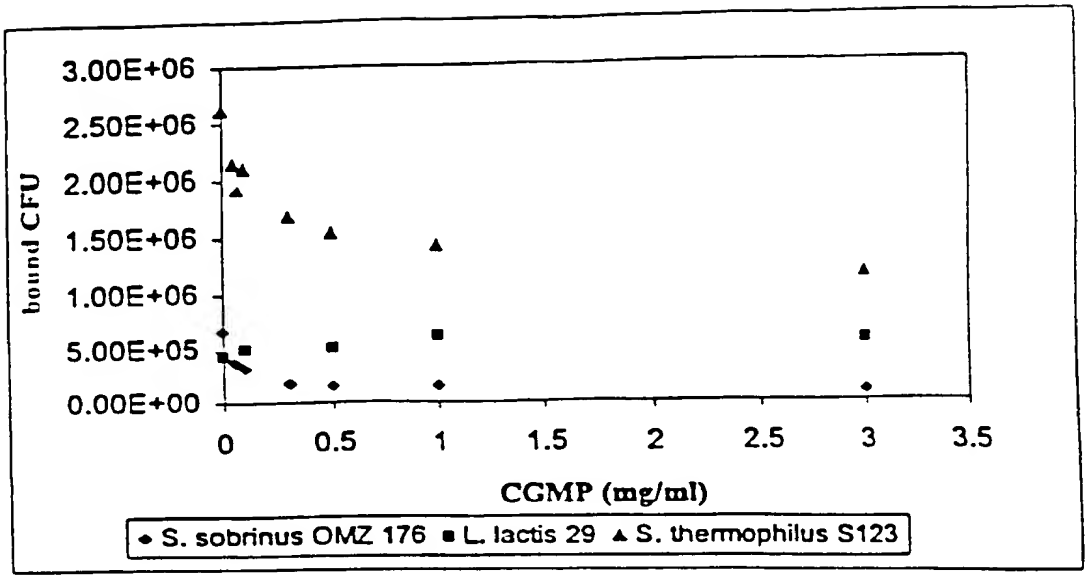


Figure 2.

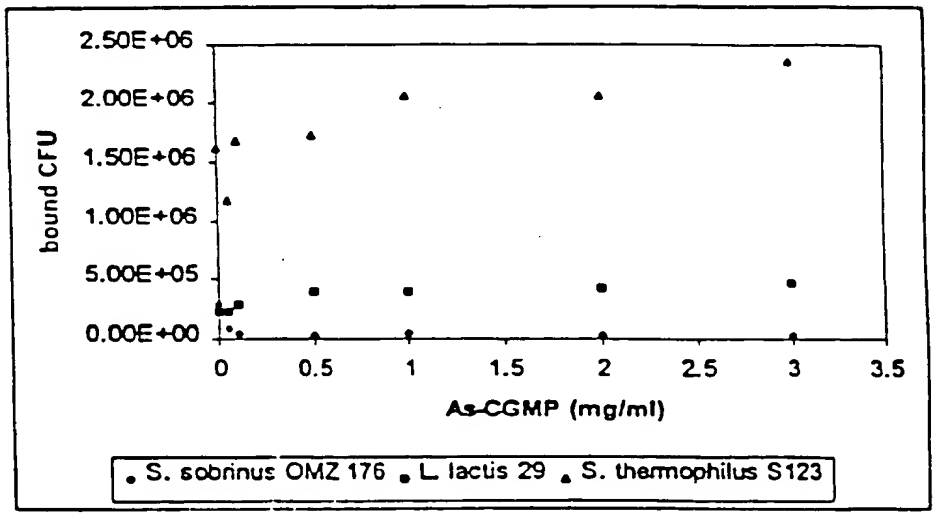


Figure 3.

119 F.3d 1559
43 U.S.P.Q.2d 1398
(Cite as: 119 F.3d 1559)

▷

United States Court of Appeals,
Federal Circuit.

The REGENTS OF THE **UNIVERSITY** OF **CALIFORNIA**, Plaintiff-Appellant,
v.
ELI LILLY AND COMPANY,
Defendant-Appellee.

No. 96-1175.

July 22, 1997.
Rehearing Denied; Suggestion for Rehearing In Banc Declined Oct. 24, 1997.

Regents of university which held patents relating to recombinant DNA technology brought infringement action against manufacturer of human insulin. The United States District Court for the Southern District of Indiana, S. Hugh Dillin, J., entered judgment for manufacturer on grounds that manufacturer did not infringe patents, that asserted claims of one patent were invalid, and that both patents were unenforceable. Regents appealed. The Court of Appeals, Lourie, Circuit Judge, held that: (1) transfer of action to district which directed pretrial proceedings was not barred by Eleventh Amendment; (2) transfer of venue was not abuse of discretion; (3) first patent was invalid for failure to comply with statutory written description requirement; (4) patent applicant did not engage in inequitable conduct by misrepresenting type of plasmid used in examples of patent application; (5) first patent was not unenforceable under doctrine of unclean hands; (6) manufacturer did not infringe second patent; and (7) patent applicant did not engage in inequitable conduct by failing to disclose reference that was cumulative.

Affirmed in part and reversed in part.

West Headnotes

[1] Federal Courts ⚿265
170Bk265 Most Cited Cases

Transfer of state university's patent infringement claim against manufacturer of human insulin to district court in another state did not violate Eleventh Amendment, as state itself asserted claim and did not have any claims asserted against it. U.S.C.A. Const.Amend. 11.

[2] Federal Courts ⚿110
170Bk110 Most Cited Cases

District court in Indiana, which conducted pretrial proceedings in consolidated cases relating to recombinant DNA technology, did not abuse its discretion by transferring venue for trial on merits, in patent infringement case, from district court in California to itself, even though Indiana court emphasized judicial economy over other factors, which court found did not favor either party. 28 U.S.C.A. § 1404(a).

[3] Federal Courts ⚿101
170Bk101 Most Cited Cases

Consideration of interest of justice, which includes judicial economy, may be determinative to particular motion to transfer venue, even if convenience of parties and witnesses might call for different result. 28 U.S.C.A. § 1404(a).

[4] Federal Courts ⚿915
170Bk915 Most Cited Cases

Patent infringement plaintiff waived claim that transfer of its action by district court which conducted pretrial proceedings in consolidated cases, for trial on merits before that court, was barred by statute, where plaintiff failed to raise claim in opening brief on appeal from final judgment, notwithstanding fact that plaintiff asserted claim in petition for mandamus seeking to vacate transfer order for consolidation of discovery. 28 U.S.C.A. § 1407(a); F.R.A.P.Rule 28(a)(6), (c), 28 U.S.C.A.

[5] Patents ⚿314(5)
291k314(5) Most Cited Cases

[5] Patents ⚿324.5
291k324.5 Most Cited Cases

Whether patent specification complies with statutory written description requirement is question of fact, which Court of Appeals reviews for clear error on appeal from bench trial. 35 U.S.C.A. § 112

[6] Patents ⇐99
291k99 Most Cited Cases

To fulfill statutory written description requirement, patent specification must describe invention and do so in sufficient detail that one skilled in the art can clearly conclude that inventor invented claimed invention. 35 U.S.C.A. § 112.

[7] Patents ⇐98
291k98 Most Cited Cases

Patent applicant complies with statutory written description requirement by describing invention, with all its claimed limitations, not that which makes it obvious, and by using such descriptive means as words, structures, figures, diagrams, and formulas that set forth claimed invention. 35 U.S.C.A. § 112.

[8] Patents ⇐98
291k98 Most Cited Cases

Adequate written description of DNA that is subject of patent requires precise definition, such as by structure, formula, chemical name, or physical properties, not mere wish or plan for obtaining claimed chemical invention, and, thus, adequate written description of a DNA requires more than mere statement that it is part of invention and reference to potential method for isolating it but requires description of DNA itself.

[9] Patents ⇐99
291k99 Most Cited Cases

Claim of patent directed to recombinant procaryotic microorganism modified to encode human insulin was invalid, because patent specification did not fulfill statutory written description requirement; although specification provided adequate written description of rat cDNA, it provided only general method of producing human insulin cDNA, not written description of human insulin cDNA, as required by asserted claim. 35 U.S.C.A. § 112.

[10] Patents ⇐98
291k98 Most Cited Cases

Claims of patent relating to recombinant DNA technology which generically recited cDNA encoding vertebrate insulin, claim which was directed generically to cDNA encoding mammalian insulin, and dependent claims which recited cDNA encoding vertebrate insulin did not adequately describe claimed invention for plasmid and microorganism that produced human insulin, notwithstanding disclosure of particular species within scope of those generic claims. 35 U.S.C.A. § 112.

[11] Patents ⇐99
291k99 Most Cited Cases

Patent specification's written description of invention involving chemical genus, like description of chemical species, requires precise definition, such as by structure, formula, or chemical name, of claimed subject matter sufficient to distinguish it from other materials. 35 U.S.C.A. § 112.

[12] Patents ⇐98
291k98 Most Cited Cases

Description requirement of patent statute requires description of invention, not indication of result that one might achieve if one made that invention. 35 U.S.C.A. § 112.

[13] Patents ⇐98
291k98 Most Cited Cases

Description of genus of cDNAs referred to in patent may be achieved by means of recitation of representative number of cDNAs, defined by nucleotide sequence, falling within scope of genus or of recitation of structural features common to members of genus, which features constitute substantial portion of genus. 35 U.S.C.A. § 112.

[14] Patents ⇐97
291k97 Most Cited Cases

District court abused its discretion in finding that applicant for patent relating to recombinant DNA technology engaged in inequitable conduct before Patent and Trademark Office (PTO) by violating National Institutes of Health (NIH) guidelines on use of plasmids and misrepresenting type of plasmid used in examples of patent application, absent evidence that noncompliance with guidelines or distinction between plasmid named in examples and plasmid actually used would have been considered material by reasonable patent examiner.

[15] Patents ⚿97
291k97 Most Cited Cases

Determination of inequitable conduct in obtaining patent is committed to district court's discretion, and Court of Appeals thus reviews district court's judgment for abuse of discretion.

[16] Patents ⚿324.54
291k324.54 Most Cited Cases

To overturn discretionary ruling of district court regarding inequitable conduct in applying for patent, appellant must establish that ruling is based on clearly erroneous findings of fact or on misapplication or misinterpretation of applicable law, or evidences clear error of judgment on part of district court.

[17] Patents ⚿97
291k97 Most Cited Cases

Alleged patent infringer asserting inequitable conduct defense must demonstrate by clear and convincing evidence that applicant or applicant's attorney either failed to disclose material information or submitted false material information to Patent and Trademark Office (PTO) and that applicant or attorney did so with an intent to deceive PTO; information is material if reasonable examiner would have considered it important to patentability of claim.

[18] Patents ⚿97
291k97 Most Cited Cases

Patent relating to recombinant DNA technology was not unenforceable under doctrine of "unclean hands," based on applicant's alleged misrepresentation of type of plasmid used in examples of patent application, absent proof that misrepresentation was material.

[19] Patents ⚿250
291k250 Most Cited Cases

[19] Patents ⚿251
291k251 Most Cited Cases

Manufacturer of human insulin which used semi-synthetic DNA to yield cleavable fusion protein did not infringe, either literally or under doctrine of equivalents, patent for invention which directly expressed human proinsulin (PI); patentee surrendered coverage of constructs which expressed recombinant fusion protein to overcome prior art rejections.

[20] Patents ⚿226.6
291k226.6 Most Cited Cases

In determining whether patent has been infringed, claim must first be properly construed to determine its scope and meaning, and, second, claim as properly construed must be compared to accused device or process.

[21] Patents ⚿314(5)
291k314(5) Most Cited Cases

[21] Patents ⚿324.5
291k324.5 Most Cited Cases

Claim construction, in patent infringement action, is question of law which Court of Appeals reviews de novo; proper construction of claims is based upon claim language, specification, prosecution history, and, if necessary to aid court's understanding of patent, extrinsic evidence.

[22] Patents ⚿314(5)
291k314(5) Most Cited Cases

[22] Patents ⚿324.5
291k324.5 Most Cited Cases

Determining whether particular device infringes properly construed patent claim is question of fact which Court of Appeals reviews for clear error on appeal from bench trial.

[23] Patents ⚿226.6
291k226.6 Most Cited Cases

To prove patent infringement, patentee must show that accused device includes every limitation of asserted claim or equivalent of each limitation.

[24] Patents ⚿168(2.6)
291k168(2.6) Most Cited Cases

In construing patent claims in view of prosecution history or in deciding whether to estop patentee from asserting certain range of equivalents, court

may only explore reason (right or wrong) for objection and manner in which amendment addressed and avoided objection.

[25] Patents ⚿168(2.6)
291k168(2.6) Most Cited Cases

When patent claim has been narrowed by amendment for substantial reason related to patentability, such as to avoid prior art rejection, patentee may not assert that surrendered subject matter is within range of equivalents.

[26] Patents ⚿314(5)
291k314(5) Most Cited Cases

[26] Patents ⚿324.5
291k324.5 Most Cited Cases

Application of prosecution history estoppel in patent infringement action is question of law subject to de novo review.

[27] Patents ⚿97
291k97 Most Cited Cases

District court abused its discretion in finding that applicant for patent relating to recombinant DNA technology engaged in inequitable conduct before Patent and Trademark Office (PTO) by failing to disclose related European patent application, because, even if it was material, application was merely cumulative of materials already before PTO.

[28] Patents ⚿97
291k97 Most Cited Cases

Even where patent applicant fails to disclose otherwise material prior art reference, that failure will not support finding of inequitable conduct if reference is simply cumulative to other references, such that reference teaches no more than what reasonable examiner would consider to be taught by prior art already before Patent and Trademark Office (PTO).

Patents ⚿328(2)
291k328(2) Most Cited Cases

4,431,740. Not infringed.

Patents ⚿328(2)
291k328(2) Most Cited Cases

4,652,525. Invalid.

Harold J. McElhinny, Morrison & Foerster LLP, San Francisco, CA, argued for plaintiff-appellant. With him on the brief were Donald S. Chisum, Alan K. Palmer, Rachel Krevans, and Debra A. Shetka. Also with him on the brief were Arthur I. Neustadt, Jean-Paul Lavalleye, Marc R. Labgold, and William J. Healey, Oblon, Spivak, McClelland, Maier & Neustadt, P.C., Arlington, VA. Of counsel was Gladys H. Monroy, Morrison & Foerster LLP, San Francisco, CA.

Charles E. Lipsey, Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., Washington, DC, argued for defendant-appellee. With him on the brief were Donald R. Dunner, Howard W. Levine, and John R. Alison. Of counsel on the brief was Amy E. Hamilton, Eli Lilly and Company, Indianapolis, IN.

Before NEWMAN, LOURIE, and BRYSON, Circuit Judges.

LOURIE, Circuit Judge.

The Regents of the University of California (UC) appeal from the judgment of the District Court for the Southern District of Indiana, holding that Eli Lilly & Company (Lilly) does not infringe U.S. Patent 4,652,525 or U.S. Patent 4,431,740 in its manufacture of human insulin; that the asserted claims of the '525 patent are invalid; and that both patents are unenforceable. *Regents of the Univ. of Cal. v. Eli Lilly and Co.,* 39 USPQ2d 1225 (S.D.Ind.1995). We hold that the district court (1) properly exercised jurisdiction over this case for trial on the merits, (2) did not err in concluding that the asserted claims of the '525 patent are invalid for failure to provide an adequate written description of the subject matter of the asserted claims, and (3) did not clearly err in finding that Lilly did not infringe the '740 patent. We further hold that the district court (4) abused its discretion in holding that the '525 and '740 patents are unenforceable. We therefore affirm-in-part and reverse-in-part.

BACKGROUND

In 1990, UC brought this action in the Northern District of California, alleging that Lilly was infringing claims 1, 2, and 4-7 of the '525 patent under the doctrine of equivalents and infringing claims 2-3, 5-6, 8-10, and 13- 14 of the '740 patent, either literally or under the doctrine of equivalents. Lilly responded that it does not infringe any of the asserted claims, that the asserted claims are invalid, and that the patents are unenforceable. Lilly did not assert any counterclaims against UC.

The patents in suit relate to recombinant DNA technology [FN1] and, more specifically, to recombinant plasmids and microorganisms that produce human insulin, a protein involved in the regulation of sugar metabolism. A person unable to produce insulin is afflicted with diabetes. Prior to the development of recombinant techniques for the production of human insulin, diabetic patients were treated with injections of animal insulin, which often caused allergic reactions. Human insulin produced by recombinant methods is less likely to produce such reactions. It consists of two separate amino acid chains, a 21-amino acid A chain and a 30-amino acid B chain, which are linked only by disulfide bonds. Healthy people produce insulin *in vivo* via the terminal enzymatic cleavage of preproinsulin (PPI) to yield proinsulin (PI), a single amino acid chain consisting of the A and B chains, linked by a sequence of additional amino acids that positions the A and B chains so that the disulfide bonds are readily formed. The PI is then further cleaved to liberate the linking sequence and yield insulin.

> FN1. For a detailed discussion of recombinant DNA technology, see *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1207-08 n. 4, 18 USPQ2d 1016, 1022 n. 4 (Fed.Cir.1991) and *In re O'Farrell*, 853 F.2d 894, 895- 99, 7 USPQ2d 1673, 1674-77 (Fed.Cir.1988) and references therein.

The '525 patent, the application for which was filed in May 1977, was based upon the determination of the PI and PPI cDNA sequences found in *rats*. Claim 1 of that patent ***1563** reads as follows: "A recombinant *plasmid* replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a *vertebrate*, which mRNA encodes insulin." (emphasis added). Claim 2 relates to a recombinant procaryotic *microorganism* containing *vertebrate* insulin-encoding cDNA. Claims 4 and 5 depend from claim 2, and are limited, respectively, to *mammalian* and *human* insulin cDNA. Claim 6 depends from claim 1 and requires that the plasmid contain "at least one genetic determinant of the plasmid col E1." Claim 7 depends from claim 2 and requires that the microorganism be of a particular strain.

The '740 patent, the application for which was filed in September 1979, was based upon the determination of *human* PPI and PI cDNA sequences and the development of "tailoring" techniques for the incorporation of human PI cDNA into a recombinant plasmid. Using these techniques, a specific semi- synthetic DNA may be incorporated into a suitable transfer vector. Using one such tailoring technique, the human PI cDNA and the plasmid into which it is incorporated may be modified so that they contain complimentary oligo-dC and oligo-dG ends, which facilitate the formation of the recombinant plasmid. Independent claim 2 of the '740 patent reads: "A DNA transfer vector *comprising* an inserted cDNA *consisting essentially of* a deoxynucleotide sequence coding for human proinsulin, the plus strand of said cDNA having a defined 5' end, said 5' end being the first deoxynucleotide of the sequence coding for said proinsulin." (emphasis added). Dependent claim 3 is directed, *inter alia*, to a recombinant microorganism containing the transfer vector of claim 2. Claim 5 reads: "A DNA transfer vector *comprising* a deoxynucleotide sequence coding for human proinsulin *consisting essentially of* a plus strand having the sequence: [nucleotides that encode human proinsulin, described in structural terms]." (emphasis added). Claim 6 depends from claim 5 in the same manner that claim 3 depends from claim 2: it is directed to a recombinant microorganism containing the transfer vector of claim 5. Claim 8 is directed to an example of a human PI-encoding recombinant plasmid described in the specification; and claims 9 and 10, to microorganisms containing that plasmid. Claims 13 and 14 are directed to a subset of the transfer vector genus of claim 5 and accordingly depend from claim 5.

Lilly makes human PI using a semi-synthetic DNA to yield a cleavable *fusion protein* [FN2] that consists of a bacterial protein, a "cleavable linkage" consisting of a single methionine residue, and human PI. After the fusion protein is produced, the desired human PI is obtained by cleaving it from the remainder of the fusion protein.

> FN2. For a detailed discussion of fusion proteins, see *Schendel v. Curtis*, 83 F.3d 1399, 1400 & n. 3, 38 USPQ2d 1743, 1744 & n. 3 (Fed.Cir.1996).

In 1992, pursuant to 28 U.S.C. § 1407 (1994), the Judicial Panel on Multidistrict Litigation (JPML) consolidated this case with five other related cases for pre-trial proceedings in the District Court for the Southern District of Indiana. *In re Recombinant DNA Tech. Patent and Contract Litig.*, No. 912 (J.P.M.L. Feb. 19, 1992). UC petitioned this court for a writ of mandamus, seeking to vacate the transfer order as barred by the Eleventh Amendment and inconsistent with various prior decisions in the consolidated cases, including two decisions of the District Court for the Northern District of California in this case. *See In re Regents of the Univ. of Cal.*, 964 F.2d 1128, 1131-32, 22 USPQ2d 1748, 1751-52 (Fed.Cir.1992) . We denied UC's petition, holding that the transfer did not force unconsented suit upon UC and thus was permissible for purposes of pretrial discovery. *Id.*, at 1134, 964 F.2d 1128, 22 USPQ2d at 1754.

In 1994, responding to Lilly's pretrial motion, the District Court for the Southern District of Indiana transferred venue to itself for trial on the merits pursuant to 28 U.S.C. § 1404(a) (1994). After conducting a bench trial, the court issued a memorandum opinion in which it ruled, *inter alia*, that (1) Lilly does not infringe the asserted claims of either patent, 39 USPQ2d at 1228-39, (2) the asserted claims of the '525 patent, those directed ***1564** to mammalian, vertebrate, and human cDNA, are invalid for lack of an adequate written description, *id.* at 1239-41, and (3) both patents are unenforceable due to inequitable conduct on the part of UC, *id.* at 1247-58. UC appeals from these rulings. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1) (1994).

DISCUSSION

A. *Jurisdiction and Venue*

[1] As a preliminary matter, UC argues that the District Court for the Southern District of Indiana lacked jurisdiction to hear this case on the merits and was an inappropriate venue for trial. UC first argues that the Eleventh Amendment deprives the Indiana court of jurisdiction. Specifically, UC asserts that by choosing to bring suit in the District Court for the Northern District of California, it waived its Eleventh Amendment immunity only in California federal courts. Relying on *Port Authority Trans-Hudson Corp. v. Feeney*, 495 U.S. 299, 307, 110 S.Ct. 1868, 1873-74, 109 L.Ed.2d 264 (1990), UC argues that the Eleventh Amendment bars the transfer of this case for trial on the merits. Lilly responds that the Eleventh Amendment is inapplicable where, as here, a state asserts a claim and no counterclaim against the state is involved. We agree with Lilly that the Eleventh Amendment does not preclude trial in Indiana.

The Eleventh Amendment provides that: "The Judicial power of the United States shall not be construed to extend to any suit in law or equity, commenced or prosecuted against one of the United States by Citizens of another State, or by Citizens or Subjects of any Foreign State." U.S. Const. amend. XI. The Supreme Court has recently confirmed that "the reference to actions 'against one of the United States' encompasses not only actions in which a State is named as a defendant, but also certain actions against state agents and state instrumentalities," such as UC. *Regents of the Univ. of Cal. v. Doe*, 519U.S. 425, ----, 117 S.Ct. 900, 903, 137 L.Ed.2d 55 (1997); *see also BV Eng'g v. Univ. of Cal.*, 858 F.2d 1394, 1395, 8 USPQ2d 1421, 1422 (9th Cir.1988).

The question raised by this case is whether it is one that has been brought "against" UC. In deciding this question, we are aided by the Supreme Court's guidance in its opinion in *United States v. Peters*, 9 U.S. (5 Cranch) 115, 3 L.Ed. 53 (1809) (Marshall, C.J.). In that case, the Court declined to apply the Eleventh Amendment to bar a suit instituted against the heirs of a deceased state treasurer. The Court stated:

> The right of a state to assert, as plaintiff, any interest it may have in a subject, which forms the matter in controversy between individuals, in one

> of the courts of the United States, is not affected by [the Eleventh] amendment; nor can [the amendment] be so construed as to oust the court of its jurisdiction, should such claim be suggested. The amendment simply provides, that no suit shall be commenced or prosecuted against a state. The state cannot be made a defendant to a suit brought by an individual; but it remains the duty of the courts of the United States to decide all cases brought before them by citizens of one state against citizens of a different state, where a state is not necessarily a defendant.

Id. at 139. This case involves a state's assertion of a claim rather than a state being a defendant.

In the *Feeney* case relied on by UC, the Court applied the Eleventh Amendment because a claim for damages was asserted "against" a state instrumentality. The *Feeney* Court noted that "a State's Constitutional immunity encompasses not merely *whether* it may be sued, but *where* it may be sued," 495 U.S. 299, 307, 110 S.Ct. 1868, 1873-74, 109 L.Ed.2d 264 (quoting *Pennhurst State Sch. & Hosp. v. Halderman,* 465 U.S. 89, 99, 104 S.Ct. 900, 907, 79 L.Ed.2d 67 (1984)), but the Court did not construe the Eleventh Amendment to apply to suits in which a state is solely a plaintiff, as UC is here. In fact, we do not believe that the Court has ever so construed the Eleventh Amendment. This is because the Eleventh Amendment applies to suits "against" a state, not suits by a state. Thus, we need not determine whether UC waived its immunity only in California, because this case does not create an Eleventh ***1565** Amendment jurisdictional issue concerning which the question of waiver even arises. This case only involves UC's patent infringement claims and Lilly's defenses; it does not involve any claim or counterclaim *against* UC that places UC in the position of a defendant. Accordingly, we conclude that the Eleventh Amendment does not deprive the Indiana district court of jurisdiction in this case.

[2] UC next argues that, under the law of the regional circuit to which appeal from the trial court would normally lie, the Indiana court abused its discretion by, as the court stated, transferring venue for trial on the merits from the California court to itself. *See Heller Fin., Inc. v. Midwhey Powder Co.,* 883 F.2d 1286, 1293 (7th Cir.1989) (applying the abuse of discretion standard of review); *Lou v. Belzberg,* 834 F.2d 730, 739 (9th Cir.1987) (same). Specifically, UC argues that the Indiana court abused its discretion by, *inter alia,* affording too much weight to the element of judicial economy in granting Lilly's motion to transfer the case to Indiana. [FN3] Lilly responds that the court acted within its discretion by retaining the case for trial and that it properly considered and weighed the relevant factors before deciding to do so.

> FN3. UC also argues that the Indiana court abused its discretion by erroneously determining that UC could have brought this suit in Indiana without the state of California's consent, by overruling inconsistent decisions of the California district court, and by failing to give special weight to UC's choice of forum. We have considered these arguments and do not find them to be persuasive.

[3] We agree with Lilly that the court did not err on this point. A federal district court may "[f]or the convenience of parties and witnesses, in the interest of justice, ... transfer any civil action to any other district court or division where it might have been brought." 28 U.S.C. § 1404(a) (1994). The Indiana court based its decision to retain the case for trial on the merits on its finding that, although the convenience of the parties and witnesses did not favor either the Indiana or the California court, the interests of judicial economy would be served by trial in the Indiana court. Consideration of the interest of justice, which includes judicial economy, "may be determinative to a particular transfer motion, even if the convenience of the parties and witnesses might call for a different result." *Coffey v. Van Dorn Iron Works,* 796 F.2d 217, 220-21 (7th Cir.1986); *Allen v. Scribner,* 812 F.2d 426, 436-37 (9th Cir.1987) ("Because the transfer of this case undoubtedly would have led to delay, the district court did not abuse its discretion in denying Allen's motion notwithstanding possible inconvenience to the witnesses."); *Commodity . Futures Trading Comm'n v. Savage,* 611 F.2d 270, 279 (9th Cir.1979) (affirming denial of transfer motion because "[t]he district court was familiar with the case and transfer may have led to delay"). Thus, the fact that the district court ultimately afforded little or no weight to the other factors does not,

standing alone, indicate that the district court abused its discretion. On the contrary, in a case such as this in which several highly technical factual issues are presented and the other relevant factors are in equipoise, the interest of judicial economy may favor transfer to a court that has become familiar withthe issues. Accordingly, the court did not abuse its discretion by transferring the case after affording determinative weight to the consideration of judicial economy.

[4] In its reply brief, UC first raises another basis for determining that Indiana was an improper venue for trial. UC argues that 28 U.S.C § 1407(a) (1994) requires that a case transferred by the JPML for consolidated pretrial proceedings be returned for trial on the merits to the court from which it was transferred. Aware that it failed to address this issue in its opening brief in this appeal, UC contends that it adequately raised this argument when it filed its petition for mandamus seeking to vacate the transfer order for consolidation of discovery in Indiana. *See In re Regents,* 964 F.2d 1128, 22 USPQ2d 1748. Lilly first responds that UC waived this argument by failing to raise it in its opening brief in this appeal, regardless of the argument it made in its earlier petition. Lilly also maintains that the transfer was lawful, citing ***1566** *In re American Continental Corp./Lincoln Savings & Loan Securities Litigation,* 102 F.3d 1524 (9th Cir.1996), *cert. granted sub nom., Lexecon Inc. v. Milberg Weiss Bershad Hynes & Lerach,* 520 U.S. 1227, 117 S.Ct. 1818, 137 L.Ed.2d 1026, 65 U.S.L.W. 3761 (1997) (No. 96-1482), for the proposition that § 1407(a) does not prohibit a discovery transferee court from transferring a case to itself for trial if an adequate reason for that transfer exists under 28 U.S.C. § 1404(a) (1994).

We agree with Lilly insofar as it argues that UC waived its argument regarding § 1407 by failing to raise it in its opening brief in this appeal. *See* Fed. R.App. P. 28(a)(6), 28(c); *Becton Dickinson & Co. v. C.R. Bard, Inc.,* 922 F.2d 792, 800, 17 USPQ2d 1097, 1103 (Fed.Cir.1990) ("[A]n issue not raised by an appellant in its opening brief ... is waived."). UC's assertion that it adequately raised this argument when it filed its petition for mandamus is not persuasive. In denying that petition, we noted that UC expressed concern that, *inter alia,* "Lilly will maneuver to try the merits of the California actions in Indiana ... thus defeating [UC's] expectation and entitlement that the merits of the California actions will be tried in California." *In re Regents,* 964 F.2d at 1133, 22 USPQ2d at 1753. However, we declined to address UC's concern then because "[t]hese possibilities can not be evaluated in the abstract." *Id.* An assertion that the district court had actually erred was required, not the mere assertion that UC feared a potential error. We thus told UC that if it desired to contest the Indiana court's self-transfer, it would be required to raise that issue if and when the Indiana court actually transferred the case to itself. Because UC failed to do so by asserting error in a writ of mandamus or in its opening brief in this appeal, we decline to address the merits of its argument. Having determined that the Indiana court had jurisdiction and that its transfer of venue to itself under § 1404 was not, given the arguments properly before us, an abuse of that court's discretion, we address the remaining issues in UC's appeal.

B. *The '525 Patent*

1. *Validity*

The district court ruled that all of the claims of the '525 patent that UC asserted against Lilly, *viz.,* claims 1, 2, and 4-7, are invalid under § 112, ¶ 1, because the specification, although it provided an adequate written description of rat cDNA, did not provide an adequate written description of the cDNA required by the asserted claims. 39 USPQ2d at 1239-41.

[5][6][7] Whether a specification complies with the written description requirement of § 112, ¶ 1, is a question of fact, which we review for clear error on appeal from a bench trial. *Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed.Cir.1991); *Ralston Purina Co. v. Far-Mar-Co, Inc.,* 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed.Cir.1985). To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli,* 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed.Cir.1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is

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claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood,* 107 F.3d at 1572, 41 USPQ2d at 1966.

[8] An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel,* 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed.Cir.1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is ***1567** required is a description of the DNA itself." *Id.* at 1170, 25 USPQ2d at 1606.

[9] We first consider claim 5, which is specific to a microorganism containing a human insulin cDNA. UC argues that the district court clearly erred in finding that claim 5 is invalid under § 112, ¶ 1. Specifically, UC argues that a constructive or prophetic example in the '525 specification describes in sufficient detail how to prepare the claimed organism. Lilly responds that the district court properly applied the written description requirement, as this court applied it in *Fiers,* 984 F.2d at 1170-71, 25 USPQ2d at 1605-06, and thus did not clearly err in finding that the cDNA encoding human insulin required by claim 5 is not adequately described in the '525 patent.

Claim 5 is directed to a recombinant procaryotic microorganism modified so that it contains "a nucleotide sequence having the structure of the reverse transcript of an mRNA of a [human], which mRNA encodes insulin." Thus, the definition of the claimed microorganism is one that requires human insulin- encoding cDNA. The patent describes a method of obtaining this cDNA by means of a constructive example, Example 6. This example, however, provides only a general method for obtaining the human cDNA (it incorporates by reference the method used to obtain the rat cDNA) along with the amino acid sequences of human insulin A and B chains. Whether or not it provides an enabling disclosure, it does not provide a written description of the cDNA encoding human insulin, which is necessary to provide a written description of the subject matter of claim 5. The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

As indicated, Example 6 provides the amino acid sequence of the human insulin A and B chains, but that disclosure also fails to describe the cDNA. Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention. *Lockwood,* 107 F.3d at 1572, 41 USPQ2d at 1966. We had previously held that a claim to a specific DNA is not made obvious by mere knowledge of a desired protein sequence and methods for generating the DNA that encodes that protein. *See, e.g., In re Deuel,* 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1215 (1995) ("A prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein."); *In re Bell,* 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed.Cir.1993). Thus, *a fortiori,* a description that does *not* render a claimed invention obvious does not sufficiently describe that invention for purposes of § 112, ¶ 1. Because the '525 specification provides only a general method of producing human insulin cDNA and a description of the human insulin A and B chain amino acid sequences that cDNA encodes, it does not provide a written description of human insulin cDNA. Accordingly, the district court did not err in concluding that claim

5 is invalid for failure to provide an adequate written description.

[10] UC also argues that the district court erred in holding claims 1 and 2, which *generically* recite cDNA encoding vertebrate insulin, and claim 4, which is directed *generically* to cDNA encoding mammalian insulin, invalid. Dependent claims 6 and 7 similarly recite cDNA encoding vertebrate insulin. In support of this argument, UC cites the disclosure of a species (the rat insulin-encoding cDNA) within the scope of those generic claims. UC argues, citing ***1568***In re Angstadt,* 537 F.2d 498, 190 USPQ 214 (Cust. & Pat.App. 1976) and *Utter v. Hiraga,* 845 F.2d 993, 6 USPQ2d 1709 (Fed.Cir.1988), that because the '525 specification meets the requirements of § 112, ¶ 1, for a species within both of these genera, the specification necessarily also describes these genera. Lilly responds that the district court did not clearly err in finding that cDNA encoding mammalian and vertebrate insulin were not adequately described in the '525 patent, because description of one species of a genus is not necessarily a description of the genus.

[11] We agree with Lilly that the claims are invalid. Contrary to UC's argument, a description of rat insulin cDNA is not a description of the broad classes of vertebrate or mammalian insulin cDNA. A written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials. *Fiers,* 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe,* 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (Cust. & Pat.App.1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus....").

The cases UC cites in support of its argument do not lead to the result it seeks. These cases do not compel the conclusion that a description of a species always constitutes a description of a genus of which it is a part. These cases only establish that every species in a genus need not be described in order that a genus meet the written description requirement. *See Utter,* 845 F.2d at 998-99, 6 USPQ2d at 1714 ("A specification may, within the meaning of § 112 ¶ 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.") (affirming board's finding that an application that "describes in detail the geometry and components that make its *internal* pivot embodiment work" also sufficiently describes an interference count that is "silent as to the location of the pivot"). In addition, *Angstadt* is an enablement case and *Utter* involves machinery of limited scope bearing no relation to the complex biochemical claims before us.

[12] In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. *See Fiers,* 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen*). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. *See In re Wilder,* 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed.Cir.1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally

known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

[13] Thus, as we have previously held, a cDNA is not defined or described by the ***1569** mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA. *See Fiers,* 984 F.2d at 1171, 25 USPQ2d at 1606. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. [FN4] This is analogous to enablement of a genus under § 112, ¶ 1, by showing the enablement of a representative number of species within the genus. *See Angstadt,* 537 F.2d at 502-03, 190 USPQ at 218 (deciding that applicants "are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art" and that the disclosure of forty working examples sufficiently described subject matter of claims directed to a generic process); *In re Robins,* 429 F.2d 452, 456-57, 166 USPQ 552, 555 (Cust. & Pat.App.1970) ("Mention of representative compounds encompassed by generic claim language clearly is not required by § 112 or any other provision of the statute. But, where no explicit description of a generic invention is to be found in the specification ... mention of representative compounds may provide an implicit description upon which to base generic claim language."); *Cf. Gosteli,* 872 F.2d at 1012, 10 USPQ2d at 1618 (determining that the disclosure of two chemical compounds within a subgenus did not describe that subgenus); *In re Grimme,* 274 F.2d 949, 952, 124 USPQ 499, 501 (Cust. & Pat.App.1960) ("[I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.' ") (citations omitted). We will not speculate in what other ways a broad genus of genetic material may be properly described, but it is clear to us, as it was to the district court, that the claimed genera of vertebrate and mammal cDNA are not described by the general language of the '525 patent's written description supported only by the specific nucleotide sequence of rat insulin.

> FN4. We note that in claims 4, 5, and 12-14 of the '740 patent, genera of DNA sequences encoding human PI or PPI are described by reference to the structure of the claimed DNA sequences rather than by reference to their function.

Accordingly, we reject UC's argument that the district court clearly erred in finding claims 1, 2, 4, 6, and 7 invalid for failure to provide an adequate written description. Because we affirm the district court's ruling that all of the claims of the '525 patent asserted against Lilly are invalid, we need not consider whether Lilly infringed those claims. *See B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.,* 72 F.3d 1577, 1583, 37 USPQ2d 1314, 1319 (Fed.Cir.1996).

2. *Enforceability*

[14] The district court also ruled the '525 patent unenforceable on the ground of inequitable conduct. The court based this ruling on its findings that UC had violated National Institutes of Health (NIH) guidelines in order to develop the patented invention as soon as possible and had falsified material in its patent application in an effort to disguise its violation. The court noted that at the time the application that became the '525 patent was filed, NIH had certified only three plasmids for use with mammalian DNA: pSC101, pCR1, and pMB9. 39 USPQ2d at 1249. It then found that UC researchers knowingly used the uncertified pBR322 plasmid to hasten their determination of the rat PI and PPI cDNA sequences, and misrepresented that they had used pMB9, a certified plasmid, in the actual examples of their patent application. The court also found that a reasonable patent examiner would have viewed this misrepresentation as material to patentability. *Id.* at 1254.

UC argues that we should reverse the district court's ruling because it is based on a misinterpretation of the applicable law on inequitable conduct. Specifically, UC argues that

the district court improperly considered alleged misrepresentations made to the NIH and Congress, and failed to properly consider ***1570** whether the alleged misrepresentation in the patent application regarding the use of pMB9 was material to patentability. UC also argues that the district court clearly erred in finding that UC actually used pBR322 and then misrepresented that it used pMB9. In response, Lilly argues that under *General Electro Music Corp. v. Samick Music Corp.*, 19 F.3d 1405, 30 USPQ2d 1149 (Fed.Cir.1994), UC's misrepresentation was sufficient to support a finding of inequitable conduct, and that such a misrepresentation need not bear directly on patentability as long as that misrepresentation was made in an effort to obtain a patent more quickly than otherwise. Lilly also argues that the district court properly found that UC's alleged pattern of deceit before a variety of governmental bodies was sufficient to render the patent unenforceable under the broad doctrine of "unclean hands." *See, e.g., Keystone Driller Co. v. General Excavator Co.*, 290 U.S. 240, 54 S.Ct. 146, 78 L.Ed. 293, 19 USPQ 228 (1933).

[15][16] "A determination of inequitable conduct is committed to a district court's discretion. Accordingly, we review the district court's judgment for an abuse of discretion." *Kolmes v. World Fibers Corp.*, 107 F.3d 1534, 1541, 41 USPQ2d 1829, 1834 (Fed.Cir.1997) (citing *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 876, 9 USPQ2d 1384, 1392 (Fed.Cir.1988)). To overturn a discretionary ruling of a district court, "the appellant must establish that the ruling is based on clearly erroneous findings of fact or on a misapplication or misinterpretation of applicable law, or evidences a clear error of judgment on the part of the district court." *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178, 33 USPQ2d 1823, 1827 (Fed.Cir.1995).

[17] We conclude that the district court abused its discretion in holding the '525 patent to be unenforceable. An infringer asserting an inequitable conduct defense must demonstrate by clear and convincing evidence that the applicant or his attorney either failed to disclose material information or submitted false material information to the Patent and Trademark Office (PTO) and that the applicant or his attorney did so with an intent to deceive the PTO. *See Kingsdown,* 863 F.2d at 872, 9 USPQ2d at 1389. Information is material if a reasonable examiner would have considered it important to the patentability of a claim. *J.P. Stevens & Co. v. Lex Tex Ltd.*, 747 F.2d 1553, 1559, 223 USPQ 1089, 1092 (Fed.Cir.1984).

The alleged misinformation submitted to the PTO in this case consists of statements in Examples 4 and 5 of the specification that the pMB9 plasmid was used as the cloning vector for the rat cDNA when pBR322 appears to have been used. Lilly does not argue that the pMB9 plasmid was inoperable in the stated examples, only that Examples 4 and 5 should not have been stated as actual examples (even though they presumably could have been stated as constructive, *i.e.*, hypothetical, examples). Accordingly, Lilly must demonstrate that this distinction would have been considered material by a reasonable patent examiner. We conclude that it has not done so by clear and convincing evidence.

There is no reason to believe that a reasonable examiner would have made any different decision if UC had framed Examples 4 and 5 as constructive examples. *See Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1578, 224 USPQ 409, 415 (Fed.Cir.1984) ("Even if intent could be inferred, and if the examples were constructive but not disclosed to the examiner as such, [the alleged infringer] has not shown the nondisclosure to have been material, *i.e.*, important to an examiner in allowing the patent to issue."); Manual of Patenting Examining Procedure (MPEP) § 707.07(*l*) (5th ed. 1993) ("The results of the tests and examples should not normally be questioned by the examiner unless there is a reasonable basis for questioning the results."); *cf. Consolidated Aluminum Corp. v. Foseco Int'l Ltd.*, 910 F.2d 804, 808-09, 15 USPQ2d 1481, 1484 (Fed.Cir.1990) (affirming a finding of inequitable conduct based on an applicant's intentional disclosure of a "fictitious, inoperable" example and withholding of a best mode.). Moreover, the examiner would not have made any different decision if pBR322, the plasmid the district court found was actually used, was recited in the examples, because, as the record shows, the procedures described ***1571** in Examples 4 and 5 for rat insulin cDNA worked to yield the intended results irrespective of whether pMB9 or pBR322 was used. The misidentification of the plasmid was therefore not material to patentability.

Thus, no inequitable conduct occurred in the procurement of the patent.

In addition, contrary to the findings of the district court, a reasonable patent examiner would not have considered non-compliance with the NIH guidelines to be material to patentability. The district court based its finding of materiality on the theory that if the applicant had complied with the guidelines, the application might have been delayed and the applicants might not have been the first to apply for a patent on the claimed subject matter. However, such unfounded speculation is not clear and convincing evidence of materiality.

General Electro Music does not support Lilly's argument that UC's failure to have actually used pMB9 would have been material to patentability. In *General Electro Music,* we concluded that "a false statement in a petition to make special is material if, as here, it succeeds in prompting expedited consideration of the patent." 19 F.3d at 1411, 30 USPQ2d at 1154. We so concluded because, by filing a petition to make special, the applicant "requested special treatment and induced reliance on its statement that a prior art search had been conducted." *Id.* As explained above, UC's alleged mischaracterization of the pMB9 work as an actual example did not induce the examiner to act, or not to act, in reliance thereon. UC got no advantage in the patent examining process. Therefore, we conclude that the district court clearly erred in finding that the misidentification of the plasmid was material to patentability.

[18] We also reject Lilly's alternative argument that the patent is unenforceable under the doctrine of "unclean hands." This court has previously refused to afford equitable relief in that guise in the absence of proof of materiality. In *J.P. Stevens,* 747 F.2d at 1560 n. 7, 223 USPQ at 1093 n. 7, we rejected the argument that "unclean hands" could render a patent unenforceable without proof of materiality because such a "categorization is inconsistent with this court's view that materiality is a necessary ingredient of any inequitable conduct." Accordingly, there is no legal basis for the conclusion that inequitable conduct occurred in the procurement of the patent and the district court therefore abused its discretion in its conclusion that the patent was unenforceable.

C. *The '740 Patent*

1. *Infringement*

[19] The district court ruled that Lilly did not infringe claims 5-6 and 8- 10 of the '740 patent either literally or under the doctrine of equivalents, 39 USPQ2d at 1231-38, and did not infringe claims 2-3 and 13-14 of the '740 patent under the doctrine of equivalents, *id.* at 1238. After evaluating the specification and the prosecution history, and receiving extrinsic evidence, the court construed these claims to be limited to genetic constructs (*i.e.*, "plasmids" and "transfer vectors") and microorganisms from which human PI is directly expressed. Accordingly, the court found that Lilly, which does not make or use such constructs or microorganisms, but expresses a recombinant fusion protein that is later cleaved to yield human PI, did not literally infringe the asserted claims. The court further determined that Lilly did not infringe the claims under the doctrine of equivalents because claim amendments made during the prosecution of the patent application bar UC from successfully asserting that the materials Lilly uses for expressing a recombinant fusion protein are equivalent to the claims of the '740 patent.

Challenging the district court's finding of a lack of literal infringement, UC argues that the district court incorrectly interpreted the claims. Specifically, UC argues that the use of the term "comprising" in the claims indicates that a transfer vector such as that used by Lilly will infringe the claims as long as it includes the inserted cDNA encoding human PI, irrespective of the presence of other elements such as the DNA encoding the remainder of Lilly's fusion protein. Lilly responds that the district court correctly interpreted the claims in light of the prosecution history. Lilly argues that a prior art ***1572** rejection was based on the examiner's conclusion that the prior art taught how to make recombinant insulin as part of a fusion protein and that UC therefore obtained allowance of the claims by specifically disclaiming transfer vectors that encode fusion proteins.

[20][21][22][23] A determination of infringement requires a two- step analysis. "First, the claim must be properly construed to determine its scope and meaning. Second, the claim as properly construed must be compared to the accused device or

process." *Carroll Touch, Inc. v. Electro Mechanical Sys., Inc.*, 15 F.3d 1573, 1576, 27 USPQ2d 1836, 1839 (Fed.Cir.1993). The first step, claim construction, is a question of law which we review *de novo;* the proper construction of the claims is based upon the claim language, the specification, the prosecution history, and if necessary to aid the court's understanding of the patent, extrinsic evidence. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979-81, 34 USPQ2d 1321, 1329-31 (Fed.Cir.1995) (in banc), *aff'd,* 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577, 38 USPQ2d 1461 (1996). The second step, determining whether a particular device infringes a properly construed claim, is a question of fact which we review for clear error on appeal from a bench trial. *See* Fed.R.Civ.P. 52(a); *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1569, 219 USPQ 1137, 1140 (Fed.Cir.1983). In order to prove infringement, a patentee must show that "the accused device includes every limitation of the [asserted] claim or an equivalent of each limitation." *Dolly, Inc. v. Spalding & Evenflo Cos.*, 16 F.3d 394, 397, 29 USPQ2d 1767, 1769 (Fed.Cir.1994).

We agree with Lilly that UC surrendered coverage of DNA that encodes a fusion protein. The district court correctly interpreted the asserted claims to be limited to genetic constructs and microorganisms that do not include DNA coding for a fusion protein. UC argues that the direct expression of human PI and the expression of human PI via a fusion protein are both described in the patent as part of the invention of the '740 patent, but that fact doesn't change the prosecution history which indicates that UC surrendered coverage of the latter in order to overcome prior art.

[24] This surrender is best exemplified by the prosecution history relating to the claims that ultimately issued as claims 2 and 5. These claims as originally filed were directed, with varying degrees of specificity, to a DNA transfer vector *comprising* a DNA sequence coding for human PI. The word "comprising," as UC argues and as is well-established, permits inclusion of other moieties. However, during the prosecution of the patent, the examiner rejected these claims as unpatentable based on, *inter alia,* Ullrich *et al.*, 196 Science 1313 (June 17, 1977) and Villa-Komaroff *et al.*, 75 PNAS 3727 (August 1978). [FN5] The district court, essentially repeating the statements made by the patent examiner during the prosecution of the patent, found that these references taught, [FN6] respectively, the need "to combine the genetic information for the eukaryotic insulin gene with prokaryotic regulatory sequences, to obtain expression of insulin in bacteria," and "a general method for the expression and secretion of any eukaryotic protein [such as human PI] provided another protein ... will ***1573** serve as a carrier [as part of a fusion protein], by virtue of its leader sequence." 39 USPQ2d at 1232. The examiner thus rejected the claims because he believed that the prior art taught the use of recombinant eukaryotic/procaryotic fusion proteins for the production of a eukaryotic protein, including insulin, in a recombinant bacterium.

FN5. Several other publications of record before the PTO were found by the district court to teach the use of fusion proteins in the production of human PI. *See* 39 USPQ2d at 1231 n. 12. For the sake of brevity, we do not discuss them here.

FN6. UC also appears to argue that the district court clearly erred in finding that these references taught the production of human PI via a fusion protein. This argument misses the point of the analysis of prosecution history. As the Supreme Court recently noted, the question of the correctness of the examiner's rejection is "properly addressed on direct appeal from the denial of the patent, and will not be revisited in an infringement action." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, --- U.S. ----, ---- n. 7, 117 S.Ct. 1040, 1051 n. 7, 137 L.Ed.2d 146, 41 USPQ2d 1865, 1872-73 n. 7 (1997). In construing the claims in view of prosecution history or in deciding whether to estop a patentee from asserting a certain range of equivalents, a court may only explore "the reason(right or wrong) for the objection and the manner in which the amendment addressed and avoided the objection." *Id.* Thus, the district court properly accepted the examiner's arguments for the purpose of construing

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the claims in view of the prosecution history.

In an effort to overcome the rejection based on these references, UC first amended claim 2 to read, in pertinent part: "A DNA transfer vector comprising an inserted cDNA *having* a[DNA] sequence coding for human [PI]...." The word "having" still permitted inclusion of other moieties. When again confronted by a rejection based upon the same references and a later requirement that the word "having" be changed to "consisting essentially of," a narrower term, UC ultimately complied by amending claim 2 to its present form, *viz.*, "A DNA transfer vector comprising an inserted cDNA *consisting essentially of* a[DNA] sequence coding for human [PI]." Similarly, UC amended claim 5 to its present form, which reads, in pertinent part: "A DNA transfer vector comprising a[DNA] sequence coding for human [PI] *consisting essentially of* a plus strand having the sequence ...." (emphasis added). The examiner allowed these claims, noting that the required "consisting essentially of" language "excludes from the cDNA the presence of sequences other than [those coding for PI]." We agree with the district court that UC thus narrowed its claims in response to a prior art rejection to exclude the materials producing a fusion protein, as Lilly now does. UC urges us to read the examiner's statement on allowance of the claims narrowly as pertaining only to claim 2 and to exclude only DNA other than naturally-occurring human cDNA. However, that statement is not so limited; it expressly applies to claim 5 and, moreover, reflects the examiner's consistent requirement, acquiesced in by UC, that the DNA inserted in the claimed vectors code only for PI, not for a PI-containing fusion protein. [FN7]

FN7. UC's later-filed amendment pursuant to 37 C.F.R. § 1.312 (1983) ("Amendments after allowance"), in which it argued that the claims as allowed would not necessarily encompass the "trivial" oligo-dC and oligo-dG ends actually used to construct the plasmid of the '740 patent, also supports this broader reading of the examiner's statement.

We have considered all of the other arguments made by UC, including its assertion that the examiner's rejections were based on a distinction between tailored and non-tailored cDNA, but find them to be unpersuasive. In light of the prosecution history, we agree with the district court that claims 5 and 6, which contain the language added during prosecution, cannot be construed to literally cover Lilly's expression of human PI via a fusion protein. Furthermore, UC has stated in its appeal brief that, for purposes of the analysis of literal infringement, the scope of claims 8-10 is no broader than that of claims 5 and 6, and that it does not appeal the court's finding with respect to claims 8-10. Accordingly, we affirm the district court's construction of claims 5-6 and 8-10; its factual finding that Lilly does not literally infringe claims 5-6 is not clearly erroneous and is therefore also affirmed.

Regarding the district court's application of the doctrine of equivalents, UC argues that the district court improperly interpreted the prosecution history to indicate that UC had disclaimed vectors encoding fusion proteins instead of to indicate, as properly interpreted, that the claims were limited to "tailored" cDNA inserts. However, as indicated above, we find no error in the district court's interpretation of the claims and the prosecution history and hence its conclusion that Lilly does not infringe the asserted claims under the doctrine of equivalents.

[25][26] When a claim has been narrowed by amendment for a "substantial reason related to patentability," such as to avoid a prior art rejection, the patentee may not assert that the surrendered subject matter is within the range of equivalents. *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, --- U.S. ----, ---- - ----, 117 S.Ct. 1040, 1049-51, 137 L.Ed.2d 146, 41 USPQ2d 1865, 1871-73 (1997); *Insituform Techs., Inc. v. Cat Contracting, Inc.*, 99 F.3d 1098, 1107, 40 USPQ2d 1602, 1609 (Fed.Cir.1996), *cert. denied*, 520 U.S. 1198, 117 S.Ct. 1555, 137 L.Ed.2d 703 (1997); ("Prosecution history estoppel ***1574** bars the patentee from recapturing subject matter that was surrendered by the patentee during prosecution in order to promote allowance of the claims."). "The application of prosecution history estoppel is a question of law subject to *de novo* review." *Id.; see also Warner-Jenkinson*, --- U.S. at ---- - ----, 117 S.Ct. at

1049-51, 137 L.Ed.2d 146, 41 USPQ2d at 1871- 73.

As the district court properly concluded, the above-described prosecution history estops UC's '740 patent from dominating Lilly's expression of its fusion protein. As a matter of law, the material used by Lilly for expressing its fusion protein is not equivalent to that of the above-analyzed claims, or to the materials of the other asserted claims, *i.e.*, claims 2-3 and 13-14, for such an application of the doctrine of equivalents would allow UC to recapture subject matter it surrendered during the prosecution of the '740 patent. Accordingly, UC cannot meet its burden of establishing infringement under the doctrine of equivalents. The district court did not clearly err in determining that Lilly did not infringe the '740 patent, either literally or under the doctrine of equivalents.

2. *Enforceability*

[27] The district court ruled that the '740 patent was unenforceable for inequitable conduct. 39 USPQ2d at 1255-58. The court based this ruling in part on its finding that UC failed to disclose to the PTO a highly-material reference, European Patent Application No. 1929 (EPA-1929), entitled "Plasmid for Transforming Bacterial Host to Render It Capable of Polypeptide Expression" in which the expression of human somatostatin and insulin are used as examples. [FN8] The court also based its ruling on its finding that UC was made aware of the materiality of EPA-1929 when it was cited as prior art by the European Patent Office (EPO) during the prosecution of the European counterpart of the application that led to the '740 patent. The court found that under these facts, it would "draw an inference of intent to mislead," *id.* at 1257, and accordingly, found that UC had engaged in inequitable conduct.

> FN8. This application was filed by Genentech, Inc. and named Drs. Itakura and Riggs as inventors.

UC argues that it did not have a duty to disclose EPA-1929 to the PTO because it was merely cumulative of the references it had submitted to the PTO. Specifically, UC argues that EPA-1929 was cumulative of the two references on which EPA-1929 was based, which were already before the examiner when UC became aware of EPA-1929: Goeddel *et al.*, 76 PNAS 3727 (1979) and Itakura *et al.*, 198 Science 1056 (1977). [FN9] UC also argues that the district court misapplied the law on inequitable conduct by inferring an intent to deceive when the uncited reference was merely cumulative. Lilly responds that EPA- 1929 was not cumulative because, unlike the reference before the examiner, it described a specific, enabling technique for making "tailored" DNA that would encode for a fusion protein including human PI. Lilly argues that UC's assertions of subjective good faith amount to no more than a mere denial of bad faith and accordingly that the district court properly disregarded those assertions. We agree with UC that the district court clearly erred in finding that EPA-1929 was not cumulative and, accordingly, in inferring an intent to deceive.

> FN9. Drs. Itakura and Riggs, inventors of the EPA-1929 subject matter, are noted as authors on both of these articles.

[28] As stated above, we review a district court's ruling that a patent is unenforceable for inequitable conduct under an abuse of discretion standard. *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 876, 9 USPQ2d 1384, 1392 (Fed.Cir.1988). An infringer asserting an inequitable conduct defense must prove by clear and convincing evidence that the applicant or his attorney failed to disclose material information or submitted false material information to the PTO, with an intent to deceive the PTO. *See id.* at 872, 9 USPQ2d at 1389. Information is material if a reasonable examiner would have considered it important to the patentability of a claim. *J.P. Stevens & Co. v. Lex Tex Ltd.*, 747 F.2d 1553, 1559, 223 USPQ 1089, 1092 (Fed.Cir.1984). However, even where an applicant fails to disclose an otherwise material prior art reference, that failure will ***1575** not support a finding of inequitable conduct if the reference is "simply cumulative to other references," *i.e.*, if the reference teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the PTO. *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1582, 18 USPQ2d 1001, 1014 (Fed.Cir.1991).

The district court correctly found that UC knew of the materiality of EPA-1929 because the EPO considered EPA-1929 to be material to the examination of the European counterpart of the '740 patent. However, if EPA-1929 was merely cumulative of other references already before the examiner, UC's failure to cite it will not support a finding of inequitable conduct because one is justified in not submitting cumulative prior art. The record indicates that EPA-1929 was cumulative. The examiner had already noted the relevance of both the Itakura article, entitled "Expression in *Escherichia coli* of Chemically Synthesized Gene for the Hormone Somatostatin," and the Goeddel article, entitled "Expression in *Escherichia coli* of Chemically Synthesized Genes for Human Insulin." As is suggested by their respective titles and their dates of publication and submission, the work described in the two articles is essentially the same as that described in EPA-1929. In fact, the record indicates that the European patent examiner cited EPA-1929 against the European counterpart of the '740 patent, but cited the Goeddel article merely to demonstrate the state of the art and did not cite the Itakura article at all.

Lilly argues that these articles are distinguishable from EPA-1929 based on the fact that EPA-1929 also includes a claim (claim 6) directed, in part, to a plasmid encoding human proinsulin. But the inclusion of a claim is not controlling in a determination whether EPA-1929 is cumulative. What is relevant is whether EPA-1929 discloses subject matter relevant to the examination of the '740 patent application that is not taught by the Goeddel and Itakura articles. Plainly it does not. The Goeddel article and EPA-1929 *describe* in similar detail the same experiments which led to the production of a recombinant human insulin/<<beta>>-galactosidase fusion protein. That Genentech attempted to claim a plasmid encoding human proinsulin in EPA-1929 does not add to its disclosure compared with the Goeddel article. We therefore conclude that the district court clearly erred in finding that EPA- 1929 was not cumulative.

Because we conclude that the district court's finding of materiality was clearly erroneous, we also necessarily conclude that the district court clearly erred in inferring deceptive intent from the mere fact that UC did not cite EPA-1929. UC's failure to disclose the EPA-1929 reference, given its cumulative nature, is not clear and convincing evidence of inequitable conduct. Because the district court's conclusion that the '740 patent is unenforceable for inequitable conduct is based on clearly erroneous findings of materiality and intent, that conclusion is reversed.

CONCLUSION

The district court properly exercised jurisdiction over this case and did not abuse its discretion in transferring the case to itself for a trial on the merits. It did not clearly err in finding that the '525 patent does not provide an adequate written description of the subject matter of the asserted claims and thus properly held that those claims are invalid, nor did it clearly err in finding that Lilly did not infringe the asserted claims of the '740 patent. The court abused its discretion in holding that the '525 and '740 patents are unenforceable. Accordingly, the decision of the district court is

AFFIRMED-IN-PART and *REVERSED-IN-PART.*

COSTS

Costs to Lilly.

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